VOLUME 53 NUMBER 8 AUGUST 1960

PROCEEDINGS

of the

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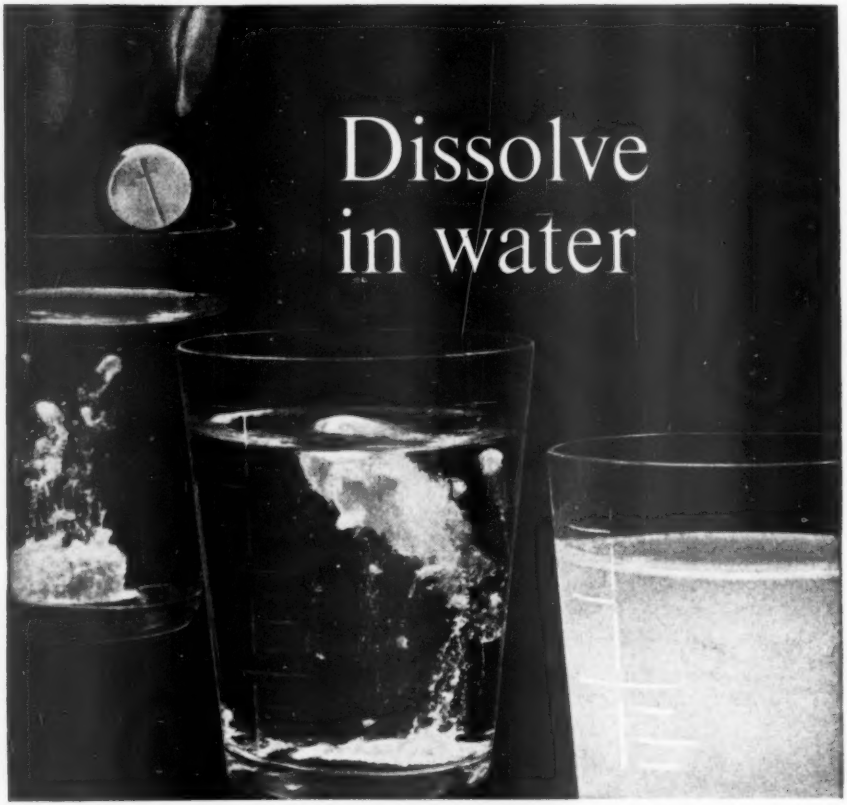

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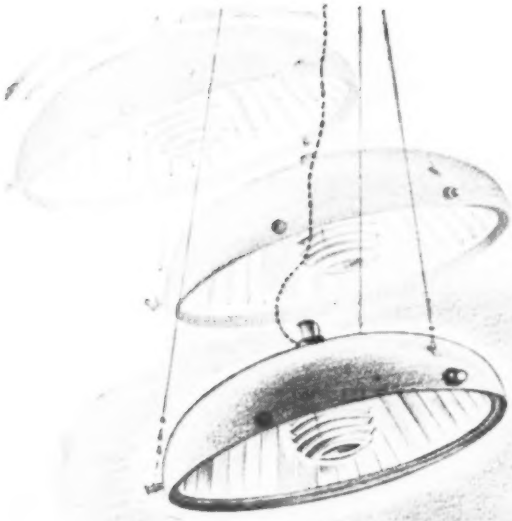

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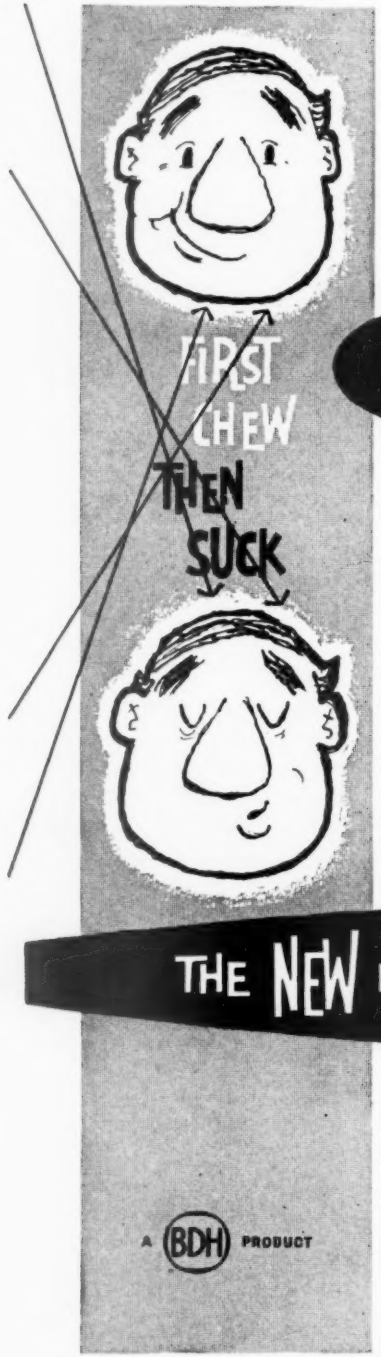

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Meeting
April 11, 1960

The Physician and the Pharmaceutical Industry in the United States

By L. W. FROHLICH
New York, U.S.A.

IT would be indiscreet of me to overlook the early spiritual ancestry claimed by the pharmaceutical industry, but in the interest of history, I must emphasize the tremendous difference between the products of the pharmaceutical art then and now. For almost two thousand years, the most reliable products of the apothecary's art—however well-intentioned the pharmacists—were either ineffective or poisonous. By 1900 pharmacology had, of course, become considerably more beneficent in its offerings. Digitalis, ergot, iodine, calomel and quinine were all recognized as having specific therapeutic effects. But their total contribution to the general welfare was at best peripheral. To speak of a pharmaceutical industry at all—even as late as 1910—is to exaggerate seriously the significance of drugs to medicine at that time. Patience, humility and understanding were more essential to the practice of medicine than the greater part of the physician's pharmacology.

A new era began with Ehrlich's synthesis of arsphenamine, with the isolation of insulin by Banting and Best, and with the techniques for the control of pernicious anæmia developed by Minot, Murphy and Whipple. But the history of the pharmaceutical industry is not quite parallel; nothing that happened before the 1930s was even a preparation for the developments that followed Dr. Gerhard Domagk's paper in 1935 which launched the sulphonamides. With the stimulus of the 2nd World War, a major industry arose within a few years. The advent of penicillin—one of England's monumental contributions to modern therapy—was the most startling evidence of this new stature. In 1943 the American pharmaceutical industry produced 29 pounds of the miraculous new powder. By July 1944—one month after D-Day—it was being produced in sufficient volume to supply adequately the Allied Invasion Forces. To-day, we are living in the midst of a pharmacological revolution. The concept of conscious, directed effort to develop specific drugs to combat specific diseases, or to fill specific needs, has captured the imagination of all.

While there was no spectacular increase in the consumption of drugs between 1930 and 1938, Fig. 1 shows the phenomenal rate of growth since then.

By 1959, ethical drug sales had increased almost three times as much as the increase in Gross National Product (Fig. 2).

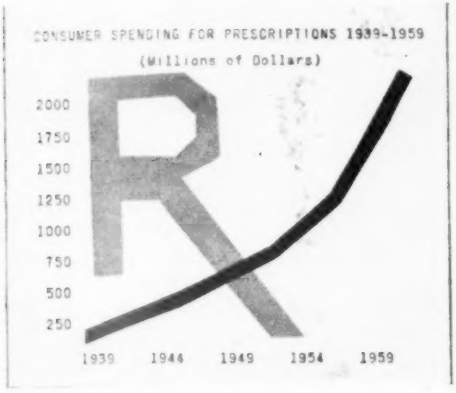

FIG. 1.—Consumer-spending for prescriptions. (Annual Prescription Survey, *Drug Topics*. New York, 1960.)

FIG. 2.—Growth of ethical drug sales 1947–1959. (U.S. Department of Commerce, and Annual Prescription Survey, *Drug Topics*. New York, 1960.

Even more important than mere growth to the character of the modern pharmaceutical industry has been the fantastic proliferation of products. Indeed, the development of new products has been far and away the largest factor in the growth. The changes in the categories of drugs available in the decade 1950–1959 are emphasized by comparison of the United States Pharmacopeia XIV, 1950, and the United States Pharmacopeia XV, 1955. The latter shows an increase of almost 250 new drugs which were not present in its predecessor. The new Pharmacopeia, now in the press and due for publication this year, will show an even more impressive figure (Fig. 3).

FIG. 3.—Changes in categories of drugs, 1950–1955. (Kramer, L. M., 1958, *Publ. Hlth. Rep., Wash.*, **73**, 929.)

A great many preparations, for example the corticosteroids and the tranquillizers, have appeared in entirely new therapeutic fields during the last decade, and provide therapeutic approaches to a multitude of diseases for which there was largely no effective treatment ten years ago.

The acceleration rate in the development of new products is enormous. The pharmaceutical industry has developed and introduced over 400 new chemicals since 1950. This amounts to a completely new product almost every week.

There has, of course, been substantial acceleration within this period; of these 400-odd new chemicals, 63 were introduced during the last year. Fig. 4 shows the number of new products introduced on a national scale in five years—

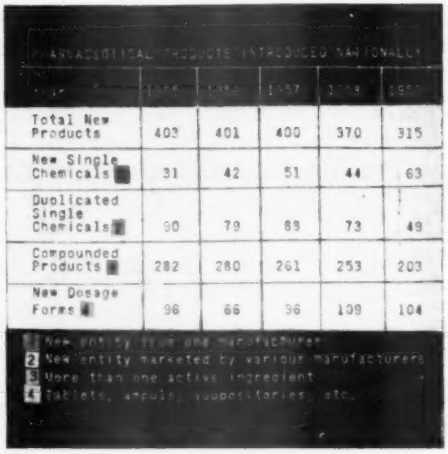

FIG. 4.—Pharmaceutical products introduced nationally, 1955–1959. (De Haen, P., 1960, *Drug Cosmet. Ind.*, **86**, 161.)

from 1955 to 1959. In addition, more than a thousand new combinations were introduced.

The product increase can be shown another way. Fig. 5 shows the effect of new products on the physician's prescribing habits in five therapeutic categories that together account for approximately one-third of prescription sales.

Fig. 5 actually understates the impact of new drugs because even where a particular category *did* exist fifteen years ago, the drugs prescribed

FIG. 5.—One-third of all prescription drugs bought by pharmacies in 1959. (Science Information Bureau, 1960, *Market Research Studies*. New York.)

to-day within that category are apt to be recent developments. For example, about 45% of those now receiving drug therapy for diabetes are on oral antidiabetic preparations, and the trend for their use seems to be upward. It is estimated that 60% of newly discovered diabetics receive oral therapy.

What I wish to point out by these statistics are the consequences of this rate of growth upon the industry responsible for it. These consequences can hardly be exaggerated. It is not too much to say that every characteristic of the pharmaceutical industry unique to it is the result of this rate of growth.

The pharmaceutical industry is a product of quick planning, on-the-spot executive decisions, rapid action, and sometimes of improvisation, although this does not imply a lack of careful thinking.

The most important characteristic of the pharmaceutical industry arising out of rapid growth is, of course, the central place that research holds in the total structure of the whole industry. As shown in Fig. 6, the pharmaceutical industry has spent about $600,000,000 on research in the past four years. This comes to about 7·5% of sales for the period. And even in so short a time, the acceleration in growth rate that is the major characteristic of the pharmaceutical industry is apparent. In 1960, it is estimated that $200,000,000 will be spent in the search for new drugs, comprising about 9% of sales. This is probably unparalleled by any industry at any time.

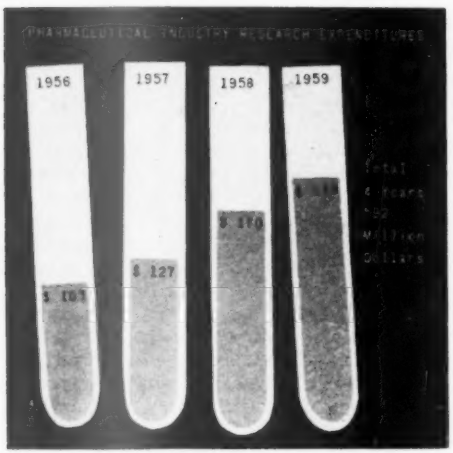

FIG. 6.—Pharmaceutical industry research expenditures. (Science Information Bureau, 1959, *New Medical Materia*, **1**, 22.)

An immense percentage of this great expenditure goes to-day into basic research—so much, indeed, that the line between basic research and applied research is becoming indistinct. For the pharmaceutical industry research is more than a sound investment; it is imperative for survival. The amount of money expended upon basic research by it is out of all proportion to that spent by other industries. In a survey made in 1955 it was found that 500 companies had contributed to fundamental research by the publication of scientific articles in the broad field of chemistry, including metallurgy, solid state and nuclear physics, and certain branches of biology and physiology. However, 59 companies accounted for over two-thirds of the total number of publications. Obviously, basic research is a major function of these companies. It is notable that more than one-fourth of these 59 companies were pharmaceutical houses.

Table I shows that the pharmaceutical industry produced two-thirds as many papers as the chemical industry, ten times its size, and it produced about as many papers as the petroleum and electrical industries, both much larger than itself. The most significant figure, perhaps, is the number of scientists per 1,000 employees—4·5 in pharmaceuticals as compared to the next industry, the chemical, with 1·27.

TABLE I.—BASIC RESEARCH BY INDUSTRY

	No. of companies	No. of employees	No. of publications	No. of scientists per 1,000 employees
Pharmaceutical	26	124,400	418	4·5
Chemical ..	109	756,000	718	1·27
Petroleum ..	115	780,000	360	0·62
Electrical ..	186	1,513,000	488	0·43

FISHER, J. C. (1959) *Science*, **129**, 1653.

The significance of research is shown even more strikingly in Fig. 7. Here we observe that the size has little to do with the intensity of effort in basic research in the pharmaceutical industry.

The smaller companies—with from 1,000 to 5,000 employees—exert as much effort proportionately in basic research as do the largest. As may be seen in the lower bar graph, this situation does not exist in the rest of the chemical industry.

Basic research is, of course, a long way from constituting the whole interest of the industry. Applied research is still the larger item in its budget. If, to-day, one were to corner the drug market as it were—if one should have, all at one time, the top prescription drugs in the ten largest drug categories—and if one should abandon research as a consequence, one's company would surely be out of business in a few years.

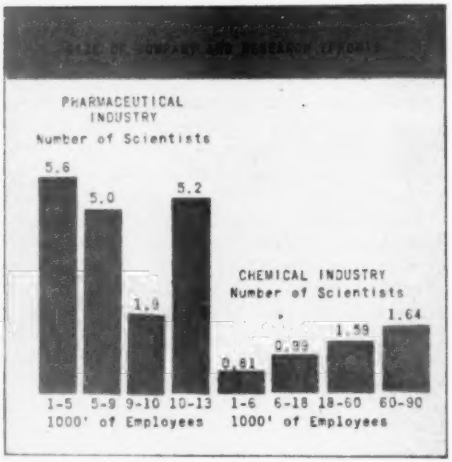

FIG. 7.—Size of company and research efforts. (Fisher, J. C., 1959, *Science*, **129**, 1653.)

The result of this unique situation is a competitive zeal in the pharmaceutical industry which would have warmed Adam Smith's heart. The whole future of the company—for good or ill—is at all times in the laboratory, and past achievement is a very shaky foundation indeed. One needs only to remember how few of the drugs used in the 1940s are still in use in the same form and manufactured by the same company to-day. Acceleration in innovation means an acceleration in obsolescence, and to-day's prescription drugs become obsolete twice as fast as they did ten years ago. In 1958 one-fifth of the drugs dropping out of the "frequently prescribed" class were less than 3 years old, and about one-half were less than 5 years old.

Where major new research findings can be anticipated, as in heart disease, it is likely that every major pharmaceutical house has some sort of relevant project going. And in these races the consolation prizes are not very consoling—rewards are very much to the swift. A new drug is hence not only a remedy or help to patients and physicians, but also a source of information—or at least stimulation—to competitors. Hence, it is not solely efficacy and availability that measures drug life from the date of introduction. The day a drug is marketed it invites other firms to do better and very often it implies a method to go about this. The result is that speed of marketing is life and death to the pharmaceutical manufacturer. The day a product is marketed he may have available, theoretically, 100% of the market. Within a relatively short time, competition will significantly limit the extent of this market. So the pharmaceutical manufacturer must always work in terms of two indeterminate lengths of time—the interval between the beginning of a research project and full production of the product of that research (if production is justified), and the interval between marketing and obsolescence. There is inherent in this situation an invitation to manufacturers to beat the clock which ticks off the hours with such finality, and there is far too little understanding of this by the uninformed, outside observers. Quite clearly, this pressure of time is of considerable advantage to the ultimate consumer. One of the most painful situations in medical history, occurring again and again, is the one in which a valuable discovery lies unrecognized for years after its first description because it fails to become generally known. In 1847 Sir Benjamin Brodie acknowledged that some means to make surgical procedures painless was among the greatest needs of mankind, but he said at the same time that he thought the wish for such a technique chimerical. But we know that ether anæsthesia had already been demonstrated the year before by Morton, and five years before by Long and Jackson. Even worse, Sir Humphry Davy had written in the year 1800—forty-seven years before—that "as nitrous oxide in its extensive operation seems capable of destroying physical pain, it may probably be used with advantage during surgical operations". And yet Sir Benjamin Brodie was one of the great surgeons of his time, and presumably one of the best informed.

But one need not go so far back. As you know, sulphanilamide—the effective part of the compound described by Domagk—had been synthesized by Paul Gelmo in 1908, and penicillin had been studied by Sir Alexander Fleming fourteen years prior to its introduction into clinical use. As useful a drug as aspirin—relatively unknown to the public in 1919—was really discovered in 1883. These intervals between discovery and general acceptance are periods of incalculable pain—of waste of human energy, of distorted and frequently shortened human lives. We are inclined, I think, to forget the positive value of urgency in pharmacology. The optimum intervals between discovery and production—between production and general use—are the shortest intervals consonant with safety and reliability. Every day these periods are prolonged *unnecessarily* may mean a day of pain, and the possibility of premature death. For the individual manufacturer, the sense of urgency stems also from the necessity of speed to ensure survival. He must communicate his successes to the only individual able to translate

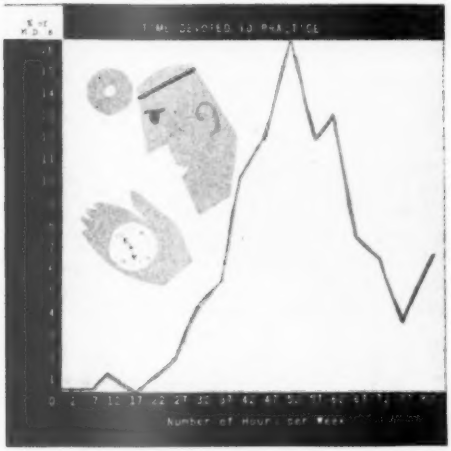

FIG. 8.—Time devoted to practice. (Parke, Davis and Co., Detroit. The Doctor's Health. *Patterns of Disease*, October 1958.)

them into public benefaction—the practising physician. Is this gentleman in the optimum condition to receive and act upon the good news? Fig. 8 makes the basic facts clear.

The average American physician works fifty hours or longer a week. In his most active period—usually before the age of 45—he is apt to work more than sixty hours a week. Reduction from this peak is ordinarily made deliberately when the physician is about 50 years old—probably on the advice of *his* physician. His is a heavy schedule. How is the physician supposed to keep up with new developments while working fifty or sixty hours a week? Fig. 9 shows the extent of the problem.

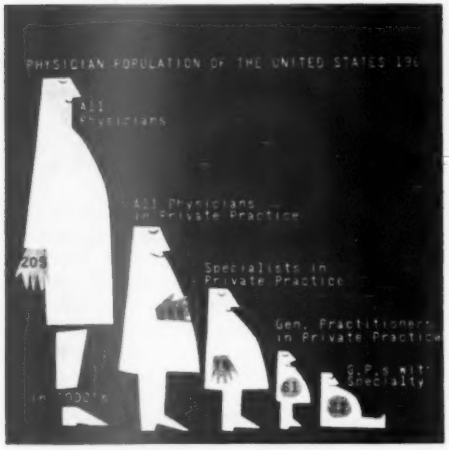

FIG. 9.—Physician population of the United States 1960. (Fisher-Stevens Medical Lists Data. Science Information Bureau; March 1960.)

Of the 205,000 practising physicians in the United States, only about 46,000 are not in private practice. This group includes hospital staff physicians, teachers in medical schools, researchers and public health officers. Of the 159,000 physicians in private practice, less than half—76,000—limit their practice to a specialty. This leaves 83,000 physicians who are in general practice, although 22,000 of these also specialize. Now it is precisely the general practitioner whose professional interests must be broadest, and to whom the greatest number of new discoveries are apt to be relevant. Fig. 10 gives us a personal

FIG. 10.—Profile of average U.S. Physician. (Parke, Davis and Co., Detroit. The Doctor's Health. *Patterns of Disease*, October 1958.)

profile of the U.S. physician in private practice.

He is the hardest-working individual in the medical profession, working a significantly greater number of hours per week than the specialist. That he has little time for leisure will be even more evident when looking at Figs. 11 and 12 which describe two typical types of practice in a one-year period.

It might be interesting at this point to learn how this busy practitioner regards his way of life. Physicians were asked if they would like their children to study medicine. The responses indicated in Fig. 13 reflect his feeling that his work is rewarding and satisfying.

FIG. 11.—One year's general practice. (Seidenstein, H. R., 1957. *N.Y. St. J. Med.*, **57**, 2827.)

And yet his need to be informed is also urgent. In the climate of opinion that has been created in the course of the last twenty years, to describe a physician as up to date is no longer to praise him highly—it is to attribute to him an indispensable characteristic. In addition to his professional conscience, public opinion forces him to this. A major force in medicine to-day in the United States is the interest that the average man takes in its progress. For something like 40% of the great number of newspaper readers, medical news is the most interesting kind of news there is. Consequently, major medical meetings are thoroughly covered by all of the major news media, and any new discovery is guaranteed extensive coverage. This is one of the most critized elements in the total medical scene to-day, and some of this criticism may be just. No physician relishes the prospect of hearing about new drugs from his patients, and this can easily happen to a busy doctor.

We have then a *new* industry, essentially, for which time is a crucial factor in every stage of its operation, which needs to make its achievements known to one of the busiest groups of people in the world—to a group which needs to know of these achievements but which works under extreme pressures itself. It is not surprising, I think, that the traditional methods of communication have proven inadequate to this situation. This is illustrated by Fig. 14.

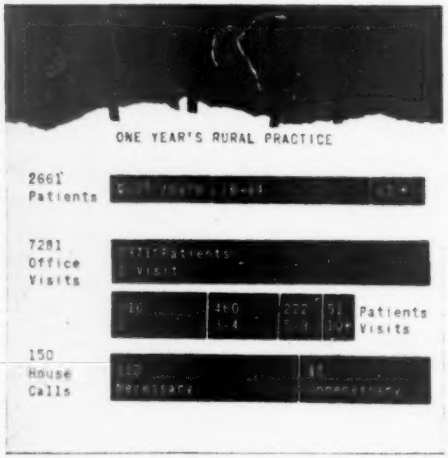

FIG. 12.—One year's rural practice. (Taubenhaus, L. J., 1955, *G.P.*, **12**, September, p. 97.)

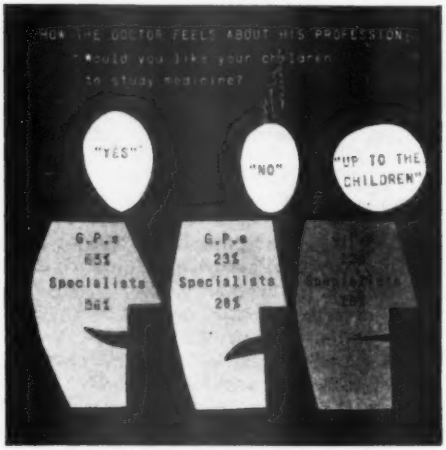

FIG. 13.—How the doctor feels about his profession. (Parke, Davis and Co., Detroit. Medical Education. *Patterns of Disease*, October 1959.)

To the question, "Where did you get the information about the last new drugs you prescribed?"—a majority of the physicians interviewed mentioned commercial sources. With regard to medical journals, however, many respondents did not distinguish between articles and advertisements. I do not mean to minimize the value of professional publications or professional meetings. They have an important place since they organize and relate available information on specific diseases and usually, in part, concern themselves with the evaluation of new data. This has always been the case. When this Society met on June 10, 1807, only one of

FIG. 14.—First knowledge of new drugs. (Ferber, R., and Wales, H. G., 1958, The Effectiveness of Pharmaceutical Promotion. Urbana, Ill.; p. 22.)

four items on the agenda was a specific—the use of cold in gout. The other three subjects discussed were chronic croup, tinea capitis, and hydrophobia in a horse—all specific conditions admitting of a variety of remedies.

For the manufacturer, the professional publications as a means of introducing new products often have the fatal disadvantage of time lag. An interval of from six months to a year and a half, or more, is customary between the submission of an article and its publication. In terms of what has already been said, one can imagine the anxiety of the manufacturer at the thought of such delay. And, from the point of view of the average physician also, journals have limitations. In the first place, there are so many of them. There are scores of major journals in the United States, containing a substantial amount of information important to the general practitioner. And one must keep in mind the quantity of new products which he must, in one way or another, evaluate.

I do not need to belabour the conclusion I think must be drawn from this survey of the relationship of the pharmaceutical industry to the modern physician. I believe that responsible medical communication is the irreplaceable bridge between them. There is no other present means of contact so swift and so concise, and we must never forget that the most rapid therapeutic application consistent with safety is to everyone's advantage.

From time to time, one may take exception to a strong pharmaceutical message—and I quote:

> "There has been much complaint of late years of growth, both in the world of trade and in that of intellect, of quackery, and especially of puffing: but nobody seems to have remarked that these are the inevitable fruits of immense competition; of a state of society, where any voice, not pitched in an exaggerated key, is lost in the hubbub. Success, in so crowded a field, depends, not upon what a person is, but upon what he seems: mere marketable qualities become the object instead of substantial ones, and a man's labour and capital are expended less in doing anything than in persuading other people that he has done it."

This was written by John Stuart Mill almost a hundred years ago, and not too much seems to have changed since then. But the pharmaceutical industry—all over the world—has good justification for making its voice heard, and for being proud of its achievements.

Again, let me say that I do not regard the present state as the ideal one, and I think the pharmaceutical industry has never refused to entertain the suggestion that things might be improved. But I wish to make it clear that its whole structure is determined by the conditions under which it has grown up, and I am absolutely convinced that the structure itself has proven its value to the public at large.

For the manufacturer of pharmaceuticals, marketing is a sequence in which each step requires fresh and crucial decisions. Products have life cycles, as Fig. 15 shows.

The period of product introduction is particularly important as it is ordinarily a period of loss, and the amount spent initially often greatly exceeds revenue from sales. Communications in this period are designed to acquaint the

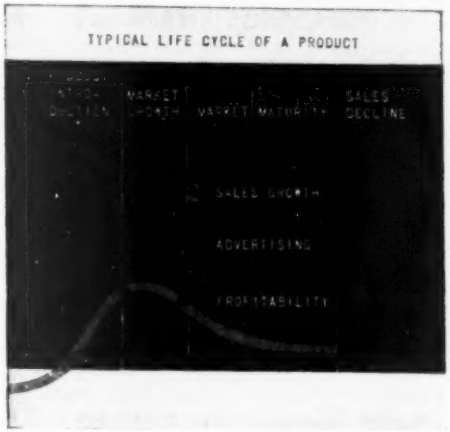

FIG. 15.—Typical life cycle of a product. (Forrester, J. W., 1959, *Harv. Business Rev.*, **37**, 100.)

largest possible number of physicians with the nature of the product and its applicability to their patient problems.

The second period is the period of market growth in which the aim is to cover the potential market as thoroughly as possible, with emphasis on the experiences gained in the first phase.

The first two periods may not be periods of intense competition (although competition does sometimes appear in the second period) but the third period—market maturity—is a critical one from every point of view, because in this period

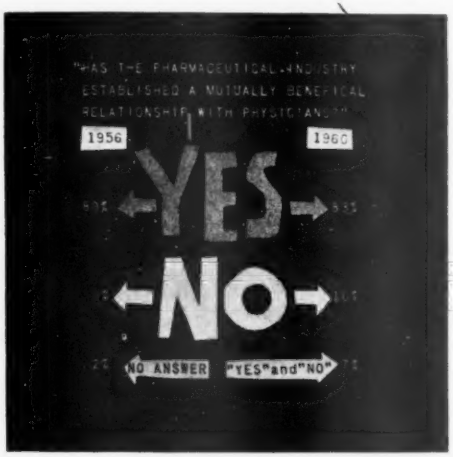

FIG. 16.—Has the pharmaceutical industry established a mutually beneficial relationship with physicians? (Science Information Bureau, 1956 and 1960, *Surveys of General Practitioners*. New York.)

similar products have usually been introduced, and at this point the physician must make his choice. As you can see, this can be the beginning of the end of the life cycle, for economic, competitive or technological reasons.

Sometimes at this point the only thing that helps product survival is the ingenuity of the manufacturer and the reputation and image he has created with the physician for quality and service. The physician respects the integrity of the manufacturer, usually because he has seen the product perform in his own clinical experience. This is why the conscientious pharmaceutical manufacturer is very hesitant ever to present an unrealistic picture. Two things work to minimize the hazard of overstated claims. One of them is concern for the manufacturer's reputation—physicians have long memories. The other factor is the development of a kind of community opinion among physicians, which is probably as reliable an index to the usefulness of a drug as there is. May we never overlook the

training of the physician: to study, observe, and form conclusions.

The last chart—Fig. 16—which is based on a study of 5,000 physicians made in 1956, and a comparison with a study made only a few weeks ago shows that the relationship between the physician and the pharmaceutical industry in the United States is an excellent one.

I would not underrate the moral problems implicit in the very existence of the pharmaceutical industry. There *is* a difference between professional and business ethics. The professional man *must* operate in terms of a very rigorous standard of professional conduct because his power in relationship to patients is so great. The businessman is of much less immediate consequence to his customers ordinarily, and hence the standard of public responsibility set for him need not be nearly so high. The drug business is in an intermediate position. Its responsibility for the health of its customers is awesome, but it is an indirect responsibility. All of its ambiguities arise from this fact. It is a business, but it is a business which is more than ordinarily susceptible—and properly so—to public attention.

However, I think the most intensive scrutiny will show that it is sound and functions properly in all of its essentials. It is not a static creation—it is a growth—determined in all of its essential characteristics by the dynamic situation in which it lives. So long as this exists, the physician-pharmaceutical industry relationship will remain essentially sound, especially since each needs the other.

Section of Experimental Medicine and Therapeutics

President—Professor W. D. M. PATON, D.M., F.R.S.

Meeting
February 9, 1960

The Renal Action of Chlorothiazide

By A. G. SPENCER, M.D., M.R.C.P.
London

CHLOROTHIAZIDE was formed as the result of an unexpected chemical reaction during the attempted synthesis of more powerful carbonic anhydrase inhibitors. Although it contains only one free sulphonamyl group, it is a stronger diuretic than acetazolamide, mainly by an action not involving carbonic anhydrase inhibition. The pattern of electrolyte excretion in the urine produced by hydrochlorothiazide is shown in Fig. 1. The principal action is an increased

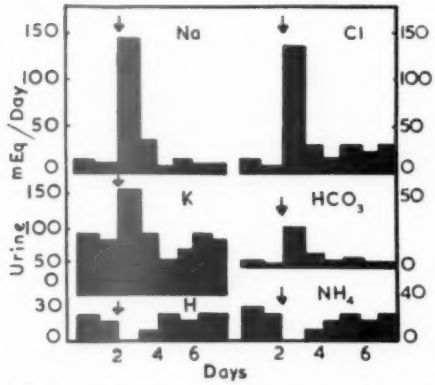

FIG. 1.—The pattern of electrolyte excretion in the urine produced by hydrochlorothiazide given at the arrow to a patient on a low salt diet.

excretion of sodium chloride, similar to a mercurial diuresis. In addition there is some carbonic anhydrase inhibition as demonstrated by the increased excretion of potassium and bicarbonate and the reduced secretion of hydrogen and ammonium ions. The mechanism of the renal action of the chlorothiazides has been extensively studied (Taggart, 1958; Buchborn and Bock, 1959) but remains unknown. The site of action of chlorothiazide in the nephron has been described by Kessler *et al.* (1959), Spencer (1959) and Vander *et al.* (1959), using the stop-flow technique.

An osmotic diuresis is produced in an anæsthetized dog by a 20% infusion of mannitol, also containing creatinine and PAH. One ureter is exposed and catheterized. The catheter is clamped for five minutes. One minute before releasing the clamp, inulin is injected intravenously. During the period of clamping, glomerular filtration is greatly reduced, and in each nephron a stationary column of fluid is in prolonged contact with the renal tubular epithelium, which performs in excess its normal transport activities. On releasing the clamp, the fluid in the nephrons is forcibly ejected and some 20 samples of 0·5–1·0 ml are collected in rapid sequence over a period of 60–90 seconds. The first two samples are unaltered pelvic urine, and later fractions come in order from the collecting ducts, distal and proximal tubules (Fig. 2). The appearance of inulin in the fractions marks the recommencement of glomerular filtration. The peak of the concentration of PAH locates proximal tubular fractions. The localization of concentration maxima and minima is remarkably precise, despite a range of transit times within the nephron population. In the distal tubules and collecting ducts, there is a maximum concentration of creatinine resulting from the reabsorption of water. Since creatinine is neither secreted nor reabsorbed by the dog's kidney, its concentration can be used as an index of water reabsorption. After the intravenous administration of chlorothiazide (10 mg/kg) the stop-flow experiment was repeated. The concentration of creatinine was now lower in all fractions, indicating a decreased reabsorption of water throughout the nephron. During stop-flow analysis the concentration of sodium remains high in the proximal tubule, but falls to 2–4 mEq/l. in the distal tubular fractions, indicating a site of active reabsorption. After

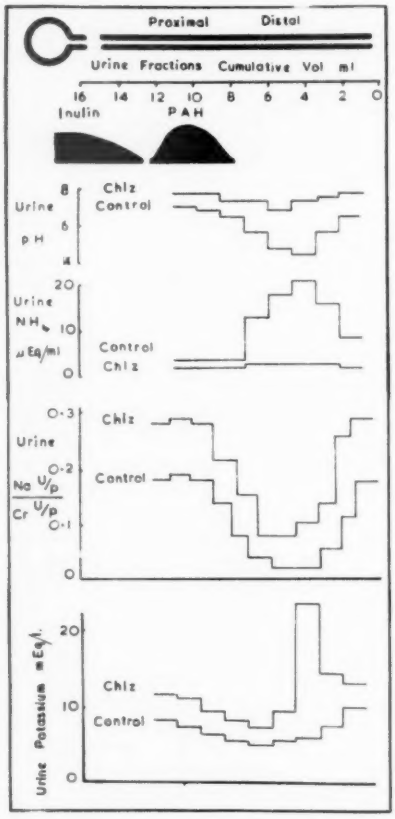

FIG. 2.—The action of chlorothiazide on electrolyte transport during stop-flow analysis.

chlorothiazide the concentration of sodium chloride in the proximal tubule is only slightly increased, and in the distal fractions the concentration is still very small. It is clear that chlorothiazide does not inhibit the ability of the distal tubules to reduce the concentration of sodium chloride in the urine. Using the U/P ratios for sodium and creatinine to correct for net transfers of water, it is evident that the main action of chlorothiazide is to inhibit the proximal and distal tubular reabsorption of sodium chloride. Chlorothiazide reduces the proximal and distal tubular reabsorption of potassium and increases the far distal secretion of this ion. In the control stop-flow experiments the distal tubular secretion of hydrogen and ammonium ions is readily demonstrated. By inhibiting carbonic anhydrase, chlorothiazide reduces the distal secretion of hydrion and ammonium, and thereby promotes the secretion of potassium ions.

The intravenous administration of chlorothiazide in the dog usually produces a fall in the inulin and creatinine clearance of some 20% (Table I). The renal plasma flow is not conspicuously changed. The fall in glomerular filtration rate occurs too quickly to be due to a reduction in the plasma or extracellular fluid volume, and its cause is uncertain. The clearance of chlorothiazide greatly exceeds that of inulin, indicating the tubular secretion of this drug. In patients on a reduced sodium chloride intake, the administration of chlorothiazide over several days is often accompanied by a 20–30% fall in the glomerular filtration rate.

TABLE I.—THE RENAL CLEARANCE OF CHLOROTHIAZIDE IN THE DOG

Period	Clearances ml/min		
	PAH	Inulin	Chlorothiazide
Control (i)	218	48	—
Control (ii)	218	46	—
Chlorothiazide (i) . .	204	39	127
Chlorothiazide (ii) . .	198	37	118

Diuretics can be distinguished by their action on the osmolar clearance and the free water clearance. Free water clearance is the result of the distal reabsorption of solutes. A water diuresis is mainly an increase in free water clearance. Chlorothiazide increases the osmolar clearance but not the free water clearance. In contrast, mercurial diuretics and acetazolamide increase both the osmolar and free water clearances.

Although chlorothiazide acts mainly on the proximal tubules, it does not interfere with the transport of glucose, amino acids or phosphate. Even when amino acids and chlorothiazide are infused into the aorta above the renal arteries, there is no demonstrable effect of chlorothiazide on amino-acid excretion (Spencer *et al.*, 1960). Chlorothiazide reduces the excretion of urates (Healey *et al.*, 1959), causing a rise in the serum uric acid, and sometimes precipitating an attack of gout. This may be due to a decrease in the filtered load of urates, or to an inhibition of the tubular secretion of uric acid.

Kidney slices, when incubated in an appropriate medium, actively take up PAH and chlorothiazide (Fig. 3). This transport can be inhibited by blocking enzyme action or by the competitive action of probenecid. Probenecid inhibits the tubular secretion of chlorothiazide, but it does not block its diuretic action. Chromatographic analysis (propanol : water : ammonia) demonstrates that chlorothiazide is excreted

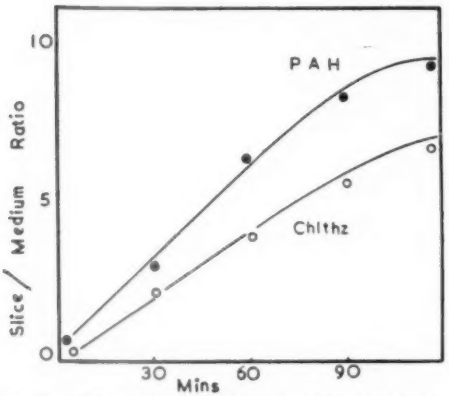

FIG. 3.—The uptake of PAH and chlorothiazide by slices of rat kidney.

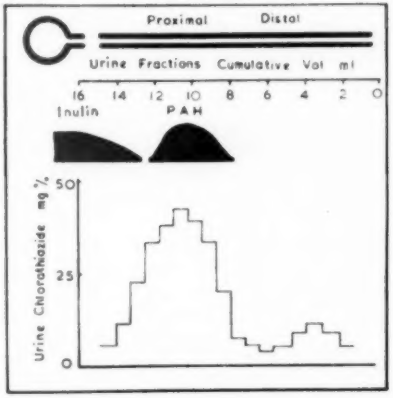

FIG. 4.—The proximal tubular secretion of chlorothiazide during stop-flow analysis.

unaltered in the urine. Although the product of hydrolysis of chlorothiazide is structurally similar to PAH, there is no evidence of enzymatic uncoupling of chlorothiazide by the kidney.

Stop-flow analysis during an infusion of chlorothiazide demonstrates a peak concentration in proximal tubular fractions (Fig. 4). Darmady (1959), using triturated hydrochlorothiazide and autoradiography of the microdissected rat nephron, has confirmed that the drug accumulates in the proximal and distal convoluted tubules.

The clinical aspects of chlorothiazide diuretics have been described by Bayliss (1959) and Havard and Fenton (1959) and in the symposia edited by Taggart (1958), and Buchborn and Bock (1959).

I should like to acknowledge the help given by my co-workers Mr. G. W. Taylor, Dr. W. R. Cattell and Miss B. Williams, and to thank Dr. E. F. Scowen, Director of the Medical Unit, St. Bartholomew's Hospital, London.

REFERENCES

BAYLISS, R. I. S. (1959) *Brit. med. J.*, i, 41.
BUCHBORN, E., and BOCK, K. D., eds. (1959) Diurese und Diuretica. Berlin.
DARMADY, M. (1959) In: Buchborn and Bock (1959) p. 182.
HAVARD, C. W. H., and FENTON, J. C. B. (1959) *Brit. med. J.*, i, 1560.
HEALEY, L. A., MAGID, G. J., and DECKER, J. L. (1959) *New Engl. J. Med.*, **261**, 1358.
KESSLER, R. H., HIERHOLZER, K., GURD, R. S., and PITTS, R. F. (1959) *Amer. J. Physiol.*, **196**, 1346.
SPENCER, A. G. (1959) Clinical Effects of Electrolyte Disturbances. London.
——, TAYLOR, G. W., and WILLIAMS, B. (1960) *Clin. Sci.* (in press).
TAGGART, J. V., ed. (1958) *Ann. N.Y. Acad. Sci.*, **71**, 321.
VANDER, A. J., MALVIN, R. L., WILDE, W. S., and SULLIVAN, L. P. (1959) *J. Pharmacol.*, **125**, 19.

The Chlorothiazide Diuretics and the Renal Handling of Water

By G. C. KENNEDY, M.B., Ph.D.
Cambridge

FOR most clinical purposes it probably does not matter whether a diuretic drug has any direct effect on the excretion of *water* by the kidney. The clinician's problem is to rid the body of excess *sodium*, and if he succeeds, water will usually look after itself. For this reason Pitts (1958) suggested that diuretics ought to be defined simply as agents which promote the renal excretion of sodium, with either chloride or bicarbonate. Now this is diametrically opposed to the views of the physiologist, at least as they are stated by Homer Smith (1957). He would define a diuretic as an agent which increases the output of osmotically free water. Such free

water is left behind by the absorption of electrolyte without an osmotically equivalent quantity of solvent, and this can only take place, so far as we know, in the distal tubule. I want to defend the practical value of knowing how different saluretic drugs influence the renal handling of water, and I shall try to show that in the strict sense chlorothiazide is not a diuretic at all, but may even be a clinically useful antidiuretic.

Soon after chlorothiazide was discovered, it was shown to cause the excretion of chloride rather than bicarbonate, and in this way to resemble the mercurials (Beyer, 1958). However, Pitts and his group (1958) found that the renal effects of mercurials and chlorothiazide were additive, so the drugs must interfere with different tubular mechanisms. One very interesting experiment by Laragh and his colleagues (1958) showed that mercurials greatly increased the excretion of free water if they were administered during a water diuresis, but chlorothiazide did not. Both drugs block the tubular reabsorption of sodium, so Laragh suggested that the mercurial compound affected only the proximal tubule, while chlorothiazide acted on the distal tubule as well. In this way, he thought, the mercurial might increase the amount of sodium reaching the normally functioning distal tubule, where reabsorption of some of this sodium would release more free water. Chlorothiazide on the other hand, by its more distal action, would prevent any such dilution of the urine. Although Laragh based his conclusions on indirect evidence, they are supported by more direct experiments using stop-flow analysis (Vander *et al.*, 1959; Kessler *et al.*, 1959).

The Antidiuretic Action of Chlorothiazide

A substitute for vasopressin in diabetes insipidus is needed for two reasons. First, occasional cases become resistant to, or intolerant of the hormone, and second, there is a familial, nephrogenic variety of the disease in which vasopressin does not work. An ideal drug would simulate the action of the hormone by promoting the tubular reabsorption of water, which is the normal method of *concentrating* the urine. However, a good second best might be to block the *dilution* of the urine by inhibiting sodium reabsorption in the distal tubule, after the manner in which chlorothiazide appeared to act. If the loss of sodium from the body could be limited, more than half the output of water in diabetes insipidus might then be saved.

Rats with severe diabetes insipidus, induced by hypothalamic lesions (Bruce and Kennedy, 1951), constantly pass urine with an osmolality of 50–100 m.osm./kg. and are therefore comparable with severe clinical diabetes insipidus. When we added chlorothiazide to their diet they excreted abnormal amounts of sodium only for the first two days of treatment. However, their urine volume fell to less than half its original value during this period, and the osmolality doubled, and these effects persisted as long as the drug was given. The rats lost no weight, on the contrary they continued to grow quite normally, so there could not have been any serious loss of electrolytes. We had to use a very large dose to obtain the antidiuretic effect, but hydrochlorothiazide and all the other still more potent derivatives now available are antidiuretic in both rats and man in normal saluretic doses (Kennedy and Crawford, 1959*a*).

Human patients with diabetes insipidus reacted in every way like rats; a detailed account has been given elsewhere (Crawford *et al.*, 1960). Our first series of 7 cases only included one of the nephrogenic variety. Through the kindness of Dr. W. J. Matheson, we have recently seen another proved case of nephrogenic diabetes insipidus respond to hydrofluomethiazide. This is what would be expected, since these cases dilute

TABLE I.—THE ÆTIOLOGY AND RESPONSE TO TREATMENT WITH CHLOROTHIAZIDE DERIVATIVES OF 8 CASES OF DIABETES INSIPIDUS

Patient	Age	Ætiology	Urine osmolality (m.osm./kg) Control	Urine osmolality (m.osm./kg) Treated	Treatment
E. G.	18	Post-traumatic	103	203 265	CF_3 50 mg b.d. HClO 50 mg b.d.
G. E.	63	Metastatic cancer	91	154	ClO 500 mg b.d.
S. W.	5	Idiopathic	60	105 93	ClO 250 mg b.d. HClO 25 mg b.d.
H. H.	26	Idiopathic	179	305	HClO 50 mg b.d.
C. S.	46	Idiopathic	88	160 178	ClO 500 mg b.d. HClO 50 mg b.d.
J. C.	46	Post-meningitis	105	171	CF_3 50 mg b.d.
D. C.	16	Nephrogenic	93	170	HClO 25 mg t.i.d.
G. E.	11	Nephrogenic	59	123	CF_3 25 mg t.i.d.

ClO = Chlorothiazide HClO = Hydrochlorothiazide CF_3 = Hydrofluomethiazide

their urine normally—it is the concentrating mechanism which seems to be at fault in the disease. Our clinical results are briefly summarized in Table I. The changes in urine volume were in inverse proportion to those in osmolality, and in most cases the daily output was approximately halved.

We were now faced with two problems. First, what caused the fall in salt output and urine volume? Secondly, could we recommend this as a treatment for nephrogenic diabetes insipidus?

The Mode of Action and Clinical Usefulness

At first the mode of action seemed to be a simple one. During the first few hours of chlorothiazide treatment patients reacted in exactly the same way as hydrated normal subjects—they excreted two to three times as much salt as normal in the same volume of urine, so the concentration of the urine naturally rose. This could be explained along the lines suggested by Laragh. During the next two days, although the increased concentration of the urine persisted, the loss of salt returned to normal, bringing the *volume* of the urine down with it. This could be explained if the amount of glomerular filtrate being presented to the distal tubule gradually decreased, and the obvious means of bringing this about would be a fall in glomerular filtration rate (G.F.R.). Blackmore (1959) commented on the fact that the chlorothiazide drugs reduce glomerular filtration rate, more than most diuretics, since this would tend to limit their usefulness in getting rid of excess salt. The endogenous creatinine clearance in two of our patients fell on continued treatment to half its control value. Further experience showed us, however, that this fall in G.F.R. frequently did not occur, and was not essential either to the conservation of salt or the reduction of urine output.

One may question the wisdom of long-term treatment with these drugs on other grounds than the undesirability of an occasional fall in G.F.R. All diuretics act by inhibiting metabolic processes; it is a mistake to think of them as *stimulating* excretion. Although chlorothiazide, even in large doses, does not cause serious tubular damage in healthy animals, we have found that even in normal doses it greatly intensifies the renal lesions caused by a potassium-deficient diet. Further cautious investigation of this kind of treatment seems justified, so long as adequate potassium supplements are given, but its interest at present is more physiological than clinical.

Physiological Implications: Antagonism Between Chlorothiazide and Adrenal Steroids

It can be shown that adrenalectomy and chlorothiazide treatment have virtually identical effects upon severe diabetes insipidus in rats (Kennedy and Crawford, 1959*b*; Kennedy, 1960), and after the urine volume has been reduced by adrenalectomy, little or no further effect can be achieved by giving chlorothiazide, so it was of interest to look for evidence that chlorothiazide and adrenal steroid might act on the same segment of the renal tubule. It was found that a combination of cortisone and deoxycortone acetate would restore the polyuria of adrenalectomized rats with diabetes insipidus. Chlorothiazide completely blocked this action of the steroids. Surprisingly, it was deoxycortone acetate and not cortisone which had the greater quantitative effect on urinary dilution, while the action of cortisone was apparently simply permissive. Chlorothiazide was therefore acting mainly as an antimineralocorticoid.

Would chlorothiazide prevent the pathological polyuria which can be induced even in normal animals by giving deoxycortone acetate for long periods? So long as the dietary load of salt is not too great it does, and it also seems to give some protection against the structural changes in the kidneys and blood vessels which usually follow deoxycortone acetate overdosage. The blocking action of the drug prevents excessive sodium reabsorption, but it does not appear, like the spirolactones, to prevent potassium loss.

REFERENCES

BEYER, K. H. (1958) *Ann. N.Y. Acad. Sci.*, **74,** 363.

BLACKMORE, W. P. (1959) *J. Pharmacol.*, **125,** 303.

BRUCE, H. M., and KENNEDY, G. C. (1951) *Proc. roy. Soc.*, Ser. B., **138,** 528.

CRAWFORD, J. D., KENNEDY, G. C., and HILL, L. E. (1960) *New. Engl. J. Med.*, **262,** 737.

KENNEDY, G. C. (1960) *J. Endocrin.* (in press).

——, and CRAWFORD, J. D. (1959*a*) *Lancet*, i, 866.

——, —— (1959*b*) *Nature, Lond.*, **184,** 1492.

KESSLER, R. H., HIERHOLZER, K., GURD, R. S., and PITTS, R. F. (1959) *Amer. J. Physiol.*, **196,** 1346.

LARAGH, J. H., HEINEMANN, H. O., and DEMARTINI, F. E. (1958) *J. Amer. med. Ass.*, **166,** 145.

PITTS, R. F. (1958) *Amer. J. Med.*, **24,** 745.

——, KRUCK, F., LOZANO, R., TAYLOR, D. W., HEIDENREICH, O. P. A., and KESSLER, R. H. (1958) *J. Pharmacol.*, **123,** 89.

SMITH, H. W. (1957) *Amer. J. Med.*, **23,** 623.

VANDER, A. J., MALVIN, R. L., WILDE, W. S., and SULLIVAN, L. P. (1959) *J. Pharmacol.*, **125,** 19.

Actions of Chlorothiazide in Hypertension

By C. T. DOLLERY, B.Sc., M.B., M.R.C.P., D. EMSLIE-SMITH, M.D., M.R.C.P., and D. F. MUGGLETON, Ph.D., B.Sc.

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CHLOROTHIAZIDE and its derivatives have attracted great interest because of their powerful saluretic effect in œdematous states and their potentiation of drugs that lower the blood pressure. Most evidence suggests that its most powerful effect is related to the sodium diuresis and, more particularly, to the fall of plasma volume that frequently accompanies sodium loss. The reduction of plasma volume makes patients more sensitive to ganglion-blocking and other pressure-lowering drugs (Dustan *et al.*, 1959). This has been confirmed by infusing salt-free dextran solution to replace the measured fall in the plasma volume in hypertensive patients treated with chlorothiazide. These infusions cancel the increase in sensitivity to a standard dose of pentolinium during treatment with chlorothiazide. A modest fall in pressure on standing is sometimes found in patients on chlorothiazide alone which is associated with the largest falls in the plasma volume (Dollery *et al.*, 1959; Wilson and Freis, 1959). As might be expected, patients who have had a previous sympathectomy are particularly sensitive to chlorothiazide.

These facts do not exclude the role of other long-term effects of sodium depletion. Conway and Lauwers (1959) have suggested that the peripheral resistance may fall after prolonged administration of chlorothiazide. We have no evidence on this point and comparatively small long-term changes in the peripheral resistance are hard to detect.

We have recently shown some new and striking effects of chlorothiazide on the action of the ganglion-blocking drug, pempidine. We used a sensitive fluorimetric method of estimating pempidine in body fluids and showed that the hypotensive response closely followed the plasma pempidine concentration, which was very predictable for a stated dose (Dollery *et al.*, 1960). When the patients were given both pempidine and chlorothiazide the plasma pempidine concentrations were much higher than before, although there was only a small increase in the hypotensive response. Patients having maintenance treatment with pempidine responded similarly: when chlorothiazide was added to the daily regime there was a two- or three-fold increase in the plasma pempidine concentration although any further fall in blood pressure was only moderate.

Chlorothiazide makes urine alkaline, which could reduce renal excretion of pempidine by non-ionic diffusion (Scribner *et al.*, 1959). In practice this was unimportant. Chlorothiazide caused only small transient changes in urinary pH (e.g. from 6 to 7). When chlorothiazide was added to a steady intravenous infusion of pempidine the excretion of pempidine hardly changed although the plasma pempidine concentration became two or three times higher than before. As a result the renal clearance was reduced to about one-third of its former value. These changes in renal pempidine clearance occurred although the urinary pH was maintained nearly constant.

Since in the presence of chlorothiazide high plasma pempidine concentrations produced a hypotensive response much less than expected, it seemed that the pharmacological activity of pempidine was altered by chlorothiazide. This was convincingly demonstrated when standard intravenous doses of pempidine were given before and after chlorothiazide. In patients having no other drugs the plasma pempidine concentration fell very rapidly. When similar intravenous doses were given after chlorothiazide the plasma concentration fell much more slowly and throughout the one-hour period of study it remained about seven times higher than before. Despite the high plasma concentrations of pempidine there was only a very slight further fall of blood pressure. It was necessary to give chlorothiazide either orally or intravenously at least an hour before the pempidine if the effect were to be produced. Intravenous injections of pempidine still give a high plasma concentration three days after the last oral dose of chlorothiazide (Fig. 1). Chlorothiazide given intravenously some hours after the last dose of pempidine provoked a rise in the plasma pempidine concentration, although there was no effect on the blood pressure.

These results led us to examine other diuretics to see if they had similar properties. Mersalyl had a similar action, although the plasma pempidine concentrations were not quite so high and the effect had disappeared three days after the dose. Acetazolamide did not alter the plasma pempidine concentration.

It seemed that chlorothiazide profoundly altered the transfer of pempidine to and from the plasma; we therefore investigated the distribution of pempidine between tissues, with and without

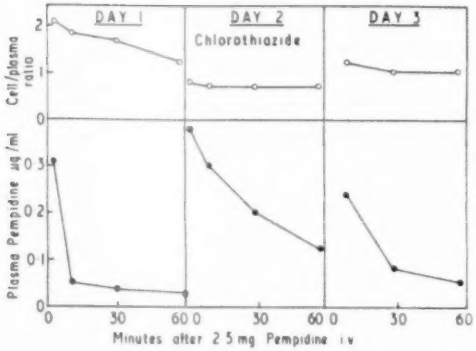

FIG. 1.—Plasma pempidine concentration and the red-cell/plasma concentration ratio for 60 minutes after an intravenous injection of 2·5 mg pempidine. On the first occasion the pempidine was given alone, on the second after two oral doses of chlorothiazide and on the third, three days after the last dose of chlorothiazide.

chlorothiazide. Since in man erythrocytes are the cells that are most easily obtained we measured the plasma and red cell concentrations of pempidine at intervals for an hour after an intravenous dose. When pempidine is given intravenously without chlorothiazide the pempidine concentration is higher in the cells than in the plasma. Five minutes after the injection the ratio of concentrations in red cells and plasma is about 2·0 : 1 and at the end of an hour it has fallen to about 1·2 : 1. Both concentrations fall rapidly throughout the hour and it seemed possible that the changes in the distribution ratio were a consequence of this, until we were able to produce a similar change *in vitro* where the changes in the plasma concentration were small. One ml solution of pempidine in saline was added to 40 ml heparinized whole blood incubated at 37° C and 4-ml samples of the mixture were taken 1, 3, 5, 10, 30 and 60 minutes after the addition of the pempidine. These samples were centrifuged and the concentration of pempidine in cells and plasma was measured separately. At one minute the ratio of pempidine concentration in cells to that in plasma was 1·3 : 1, at five minutes 2·1 : 1 and at one hour 1·2 : 1.

When an intravenous injection of pempidine was given after chlorothiazide the high sustained plasma concentration was paralleled by a slightly lower, but still high, cell concentration. The red-cell/plasma concentration ratio was now 0·7:1 and did not change throughout the hour. Identical results were obtained when whole blood was incubated with chlorothiazide for an hour before adding pempidine. Equilibrium was reached by the time of the first sample at one minute and the red-cell/plasma concentration ratio remained at 0·7:1 for the whole hour. When mersalyl was substituted for chlorothiazide both *in vivo* and *in vitro*, a constant red-cell/plasma concentration ratio of 1·0:1 was found.

Studies of distribution in the tissues of rats showed similar changes in the red-cell/plasma concentration ratio. There were also small decreases in the amount of pempidine in spleen, lung and voluntary muscle.

The most economical hypothesis to explain these results seemed to be that chlorothiazide caused pempidine to be bound to plasma proteins. Equilibrium dialysis showed that this was indeed so. Solutions of serum albumin and pempidine were allowed to equilibrate for forty-eight hours and the concentration of pempidine in both solutions was estimated fluorometrically. Equal concentrations of pempidine were found in the two compartments, showing that the drug had not interacted with the protein to any significant extent. When chlorothiazide was added to the system the concentration of pempidine in the protein solution was substantially increased, some of the drug now being bound to the protein. For concentrations of chlorothiazide in the range 1·3–24·6 µg/ml between 16 and 68% of the pempidine was bound to protein (Fig. 2).

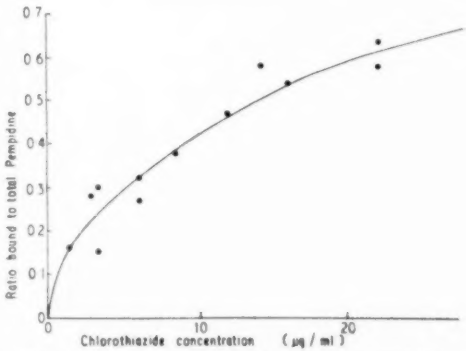

FIG. 2.—The ratio of bound to total pempidine plotted against chlorothiazide concentration in an equilibrium dialysis system containing bovine serum albumin at a concentration of 1 g/100 ml.

We do not know the precise nature of the association that occurs between chlorothiazide (or mersalyl), pempidine and protein. Chlorothiazide itself is extensively bound to plasma protein (up to 70% in our experiments) and it is possible that the protein-bound chlorothiazide becomes directly linked to pempidine, though it is difficult to accept this hypothesis. Intravenous studies showed that the effect of chlorothiazide on pempidine persisted for at least seventy-two hours, whereas the diuretic effect of chloro-

thiazide lasts for only twelve to eighteen hours and it is very unlikely that much of the drug remains in the body for as long as three days. It is possible that enough chlorothiazide is bound to protein to produce the effects we have observed but our methods of assaying chlorothiazide are not sensitive enough to detect it. Alternatively, chlorothiazide may modify the protein surface in some way so that pempidine could still be bound after the chlorothiazide has been entirely removed.

From our data on protein-binding of pempidine it is possible to explain many, but not all, of our observations with hypertensive patients. If we assume that 70% of the pempidine is bound to protein, chlorothiazide would produce high plasma pempidine concentrations with little change in the hypotensive response because the free, pharmacologically active pempidine concentration would remain about the same. The change in renal clearance of pempidine is also compatible with this degree of protein-binding if it is assumed that the bound pempidine is neither filtered at the glomerulus nor available for tubular excretion. However, it is much more difficult to reconcile protein binding of pempidine with the changes in red-cell/plasma distribution ratio caused by chlorothiazide, both *in vivo* and *in vitro*.

No satisfactory explanation can yet be given for the changes in the pempidine concentrations of red cells and plasma seen in the intravenous studies. Pempidine alone is rapidly cleared from the plasma. After chlorothiazide a large part of it is bound to protein, so the total plasma pempidine concentration decreases only slowly; but there is no reason to suppose that the diffusible fraction will not still be cleared rapidly. Presumably the fall in plasma pempidine concentration would be regulated by the rate of dissociation of the pempidine-chlorothiazide-protein complex, but then the free pempidine concentration and the hypotensive response would be very low. If this is so the high concentration of pempidine in red cells is unexplained, for this must depend upon the concentration of the unbound pempidine in the plasma. It seems probable therefore that chlorothiazide in some way also changes the affinity of red cells for pempidine.

Despite these remarkable interactions there is very little change in the pressure-lowering effect. Clinical observation suggests that when pempidine is given with chlorothiazide its action becomes more uniform and more prolonged, possibly because the large fraction that is bound to protein acts as a buffer.

It is a very curious chance, if chance it be, that two diuretics with a similar saluretic effect, mersalyl and chlorothiazide, should have such a closely similar action on the binding of pempidine to plasma protein.

Chlorothiazide is a useful adjuvant to other more potent drugs in the treatment of hypertension. The greater part of this action depends upon sodium depletion and reduction of plasma volume—an effect similar to a strict low salt diet. A subsidiary action of great theoretical, and some practical importance is the change in distribution and handling of pempidine that occurs mainly as a result of binding to plasma proteins.

REFERENCES

CONWAY, J., and LAUWERS, P. (1959) *Circulation*, **20**, 680.

DOLLERY, C. T., EMSLIE-SMITH, D., and MUGGLETON, D. F. (1960) *Brit. med. J.*, i, 521.

——, HARINGTON, M., and KAUFMAN, G. (1959) *Lancet*, i, 1215.

DUSTAN, H. P., CUMMING, G. R., CORCORAN, A. C., and PAGE, I. H. (1959) *Circulation*, **19**, 360.

SCRIBNER, B. H., CRAWFORD, M. A., and DEMPSTER, W. J. (1959) *Amer. J. Physiol.*, **196**, 1135.

WILSON, I. M., and FREIS, E. D. (1959) *Circulation*, **20**, 1028.

Meeting
May 10, 1960

The following papers were read :

Pharmacology of Reserpine-like Compounds.—Dr. M. VOGT.

Effects of Reserpine on the Electroencephalogram.—Dr. P. B. BRADLEY.

Reserpine and Mental Function.—Dr. D. M. LEIBERMAN.

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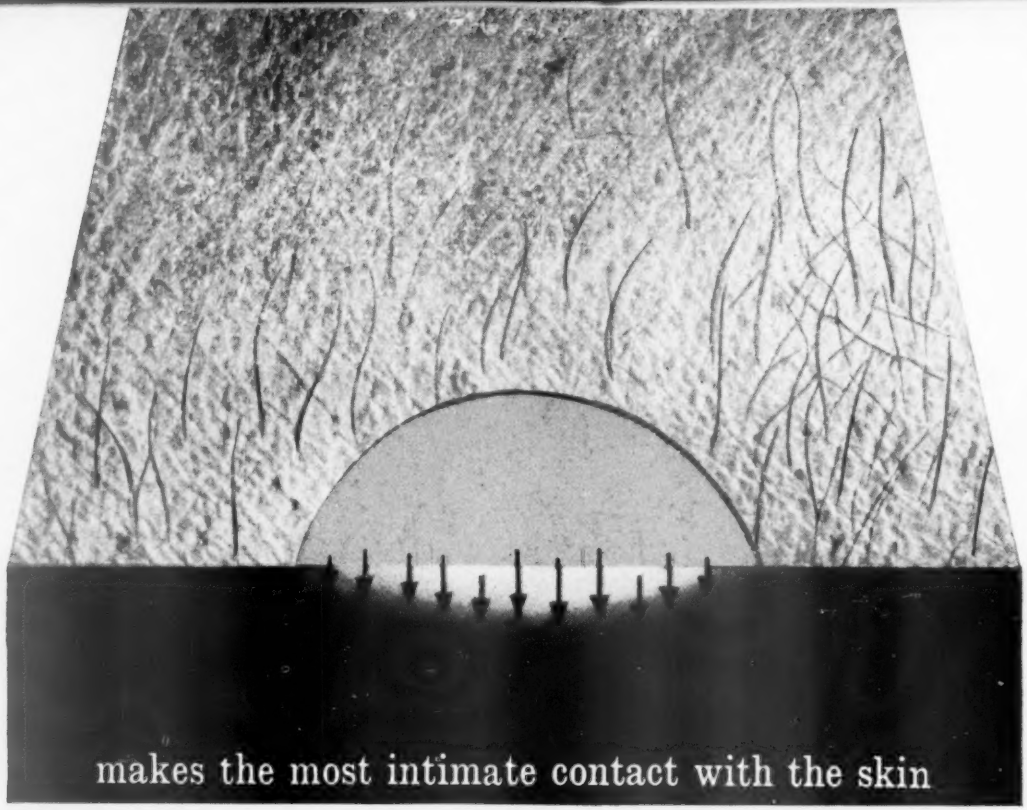

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Meeting
February 24, 1960
(continued from June *Proceedings*, p. 436)

THE following papers were also read:

The Identification of 20α-hydroxypregn-4-en-3-one in the Peripheral Blood of Pregnant Women.—Dr. R. V. SHORT.

A Simple Procedure for Investigating the Effect in Man of 1, 2, bis (3-pyridyl)-2-methyl-1-propanone ditartrate (SU4885).—Dr. W. R. BUTT, Dr. A. C. CROOKE, Dr. E. HILL and Mr. R. MORRIS.

The Effect of 1-dehydro-methyltestosterone on Growth in Children.—Dr. G. L. FOSS.

Some Characteristics of Spermatozoa Following Experimental Occlusion of the Epididymis in Rabbits.—Dr. T. D. GLOVER. To be published in full later.

A Comparison Between the Activity of Some Adrenal Steroids and Chlorothiazide in Producing Diuresis in the Rat.—Dr. P. F. D'ARCY and Miss E. M. HOWARD.

Corticotrophin Release in Man.—Dr. S. SHUSTER.

Thyroid-stimulating Activity in Human Serum.—Dr. D. S. MUNRO and Miss P. W. MAJOR. *See:* MUNRO, D. S. (1959) *J. Endocrin.*, **19,** 64.

A Pituitary-dependent Inhibitor of Glucose Uptake by Muscle in Protein Fractions of Human Plasma.—Dr. K. W. TAYLOR, Dr. L. VARGAS and Dr. P. J. RANDLE.

Hormonal Nature of Urinary Fat-mobilizing Substance.—Dr. T. M. CHALMERS, Mr. G. L. S. PAWAN and Professor A. KEKWICK. *See: Lancet*, 1960 (in press).

Meeting
March 23, 1960

ORAL HYPOGLYCÆMIC AGENTS IN THE TREATMENT OF DIABETES MELLITUS

Professor A. Loubatières (Montpellier, France)[1]: *Experimental Studies for the Tentative Use of Hypoglycæmic Sulphonamides as Prophylactic Agents against Diabetes*

It is now well established that hypoglycæmic sulphonamides, whether thiodiazole or urea derivatives, have the same mechanism of action. They have a particular influence on the beta cells of the islets of Langerhans and are inactive after total extirpation of the pancreas. A small fragment of normal pancreas (including normal islets) representing one-tenth of the initial pancreatic gland is, however, sufficient to maintain their hypoglycæmic activity (Loubatières, 1944, 1946*a*, *b*).

The administration of sulphonamide to a normal animal induces a clear-cut degranulation of the beta cells of the islets of Langerhans (Gepts *et al.*, 1955, 1956; Creutzfeldt and Finter, 1956; Volk *et al.*, 1956; Holt *et al.*, 1956; Loubatières, 1957*c*; Loubatières, Sassine, Fruteau de Laclos and Bouyard, 1957; Loubatières and Fruteau de Laclos, 1958; Kracht, 1958; Fruteau de Laclos and Loubatières, 1960) which suggests that some intraprotoplasmic insulin particles have been liberated into the circulating blood. Lacy and Hartroft (1959) have shown, with the electron microscope, that the administration of tolbutamide is followed by the loss of insulin granules from the beta cells. The degranulation is a functional one; it is reversible and within a few hours the insulin granules re-form in normal numbers (Pfeiffer *et al.*, 1957). These phenomena are seen most strikingly in the cells close to blood vessels.

Hypoglycæmic sulphonamides administered to certain animals (the rat, rabbit, dog and mouse) for several days induce hyperplasia of the islets of Langerhans and new formation of the insulin secretory beta cells (Loubatières, 1946*b*; Ashworth and Haist, 1956; Gepts *et al.*, 1956; Kracht, 1958). This hyperplasia is due in part to mitotic division of the existing beta cells, as can be shown by the use of colchicine (Kracht, 1958; Jores and Kracht, 1959), and in part, as we have found, to small islets developing in the acinar tissue (Loubatières and Fruteau de Laclos, 1958; Fruteau de Laclos and Loubatières, 1960).

These newly formed beta cells appear next to and probably have their origin from the centro-acinar cells and from the cells of certain of the excretory canaliculi. Intermediate forms be-

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tween acinar cells and endocrine cells are visible (Loubatières and Fruteau de Laclos, 1958; Fruteau de Laclos and Loubatières, 1960). From these cellular transformations it follows that the total amount of beta cell tissue increases (Ashworth and Haist, 1956) and thus the effectiveness of the endocrine tissue in the regulation of the blood sugar level becomes greater. The phenomenon of hypoglycæmia and islet hyperplasia, particularly the new formation of beta cells, is especially striking if the sulphonamide is administered through the Wirsung duct of the pancreas (Loubatières, Sassine, Mariani and Fruteau de Laclos, 1960).

By pancreatico-jugular anastomosis or cross-circulation between a donor dog treated with sulphonamide and a recipient dog receiving the pancreatic blood of the donor, it is possible to show the passage, from donor to recipient dog, of the excess insulin secreted into the blood by the pancreas of the animal treated with sulphonamide. When pancreatico-duodenal venous blood of a normal dog is transfused to a responsive recipient dog, it is more hypoglycæmically active after the administration of sulphonamide than before (Loubatières, 1946*a*; Loubatières, Bouyard and Sassine, 1958).

In addition to their action on the beta cells the hypoglycæmic sulphonamides reinforce the effects of exogenous or endogenous insulin on blood glucose (Loubatières, Bouyard, Fruteau de Laclos, Sassine and Alric, 1956; Loubatières, Bouyard, Sassine and Fruteau de Laclos, 1957; Houssay and Migliorini, 1956)—an effect which can be observed in the totally depancreatized animal.

Different hypotheses have been proposed to explain this phenomenon, notably the theory of insulinase inhibition (Mirsky *et al.*, 1956), but most authors have now discarded this. We think that potentiation of insulin, which is only observed with large doses of sulphonamide, can be explained by the liberation of insulin, previously injected or secreted, that has been fixed to certain proteins. These molecules of liberated insulin may exert their activity *in situ* or be returned to the circulation and thus become capable of exhibiting elsewhere their normal activity. Such a process of liberation of fixed insulin might be similar to the action of sulphonamides on the beta cell granules because the latter are probably complexes of insulin and protein (Loubatières, 1959*b*).

The hypoglycæmic action of the sulphonamides just described is only one aspect of their mechanism of action. These substances also possess an "*anti-diabetic action*" (Loubatières, 1946*b*, 1955, 1957*a*, *b*). By this we mean that hypoglycæmic sulphonamides can, in some conditions, reduce the fundamental cause of the diabetic state, which seems to depend upon a numerical and functional deficiency of beta cells, and in other conditions prevent the development of the diabetic state. There follows a significant rectification of the metabolic abnormalities and a tendency towards normality of the regulation of the blood sugar level.

What are the effects of prolonged treatment with sulphonamides on the dog suffering from meta-alloxan diabetes? (Loubatières, 1955; Loubatières, Bouyard and Fruteau de Laclos, 1955, 1956; Loubatières, Bouyard, Fruteau de Laclos and Sassine, 1957; Loubatières, 1957*a*, *b*; Loubatières, Bouyard, Sassine and Fruteau de Laclos, 1958.) If the diabetes is initially severe the dog may lose weight, develop ketosis and eventually die. Treatment with sulphonamide appears unable to alter this sequence. During the course of the experiment, successive pancreatic biopsies show that islets of Langerhans which had been seriously damaged before treatment with sulphonamide remain so after treatment. The beta cells are largely destroyed and are often replaced by scar tissue. The very few beta cells which escape destruction by alloxan are degranulated. No process of new formation of islet cells is seen, probably because those mother cells which might have provided the source of new beta cells have themselves been destroyed. Even if some of these survive, they will quickly be exhausted and finally damaged by their struggle against the high blood sugar which the sulphonamide is not able to reduce. The cycle maintaining the diabetic state has been set in motion and the sulphonamides cannot break it.

However, carefully controlled insulin therapy, associated with sulphonamide treatment, may enable the sulphonamide to exert its trophic action on the islets of Langerhans. The dosage of insulin can then be progressively reduced by 50–80%. In such instances a histological examination of the pancreas reveals new beta cells. These newly formed cells originate particularly from the cells of the excretory canaliculi and probably from the acinar tissue. However, endocrine tissue is fragile and not well developed. Perhaps, in such instances, the exogenous insulin comes to the aid of the sulphonamides and of the endocrine tissue of the pancreas.

On the other hand if the diabetes is of only moderate severity its development will generally be different. Treatment with sulphonamide alone during a period of some weeks can lead to a reduction of the diabetic symptoms and even to their disappearance (Loubatières, 1955; Loubatières,

Bouyard and Fruteau de Laclos, 1955, 1956; Loubatières, 1957*a*, *b*, *c*; Loubatières, Bouyard, Sassine and Fruteau de Laclos, 1958). The benefit is well shown by a rapid increase in the body weight of the animal which, before treatment with sulphonamide, tended to fall. At the end of three to eight weeks, treatment can be stopped and the animal may remain "cured". In such cases histological examination of the pancreas shows changes comparable with those induced by hypoglycæmic sulphonamides in the normal animal. Their development and intensity are, however, of lesser degree.

New beta cells appear, originating from the cells of the external secretory canaliculi and the centro-acinar cells, which become clearly identifiable and globular. Transitional forms between exocrine and endocrine cells are also visible; many small islets of Langerhans appear. Pancreatic ductules are dilated. Only if the "cure" is maintained do the islets of Langerhans develop and become well organized. The cellular reorganization of pancreatic tissue characteristic of the action of sulphonamides can therefore occur (Loubatières, Bouyard, Sassine and Fruteau de Laclos, 1958; Loubatières and Fruteau de Laclos, 1958; Fruteau de Laclos and Loubatières, 1960). These substances are most effective if treatment is undertaken early during the development of the diabetic condition.

The results of the previous existence of the meta-alloxan diabetes may nevertheless be seen in the sugar tolerance curve even when "cure" has been effected (at least at the beginning of the period of "cure"). If, however, a balanced food intake (horse-meat) is permitted, such as will maintain but not increase the body weight, the sugar tolerance curve becomes lower and lower, and finally approaches normal. The process of "cure", which has been fostered by treatment with the sulphonamide, can continue after cessation of this treatment.

Unrestricted food intake can, by contrast, induce an increase in the body weight and threaten the state of "cure" (Loubatières, 1958, 1959*c*, *d*). This has an important bearing on the treatment of the human diabetic.

We have found that the "new equilibrium" instituted by the sulphonamide treatment rests on the formation of islet beta cells which can function. These new beta cells are normal and not unduly sensitive to the action of the mechanisms which regulate the blood sugar level. In fact, the fasting blood sugar of these animals is normal (85–90 mg/100 ml). The new beta cells can be stimulated by the same dosage of hypoglycæmic sulphonamides as normal cells, since the administration of these substances induces a striking hypoglycæmia. Furthermore, these cells can be destroyed by alloxan, thus rendering diabetic once more the animal whose previous diabetes had been cured by sulphonamide treatment (Loubatières, Bouyard, Sassine and Fruteau de Laclos, 1958).

This process of "cure" or disappearance of the diabetic symptoms, fostered and induced by sulphonamides, is not confined to meta-alloxan diabetes. It has been observed in cats with meta-hypophyseal diabetes (Young, 1956).

In more recent experiments, Young *et al.* (1959) have produced a "cure" with tolbutamide or carbutamide in six cats with meta-hypophyseal diabetes fifteen to thirty-five weeks after stopping the injections of growth hormone. In the electron micrographs taken by J. D. Lever of some of their tolbutamide-treated cats, there was clear cytological evidence of a complete restoration of previously altered beta cells (Lever and Jeacock, 1960).

Another example of the possibilities of "cure" of diabetes with the use of hypoglycæmic sulphonamides is given by spontaneous diabetes in the dog. Brion and Fontaine (1959) studied the action of carbutamide in 30 cases of spontaneous canine diabetes. They concluded that the hypoglycæmic sulphonamides are inactive in advanced diabetes with ketosis and weight loss, which corresponds to the severe and neglected diabetes of the old dog. On the other hand, during the first months of induction of diabetes, when hyperglycæmia is moderately increased, the administration of sulphonamide considerably reduces the diabetic symptoms. The authors conclude: "It is surprising indeed that this amelioration is often a long-lasting one. We possess now the observation of a female dog which is still in a normal state, one year after a ten-day treatment with sulphonamide compounds. More often, relapses occurred within one to two months, but could again be reversed by administration of carbutamide."

One may now ask if the regenerative action exerted by sulphonamides on the beta cells could not be used as a tool in the prophylactic treatment of experimental diabetes. The administration of sulphonamide during the period of induction of diabetes (idio-hypophyseal diabetes) seems to oppose the establishment of meta-hypophyseal diabetes—the diabetic condition which occurs in the dog as the result of the administration over a three weeks' period of crude extract of anterior pituitary gland (Loubatières, Bouyard, Fruteau de Laclos and Sassine, 1956). Recently, Mirsky *et al.* (1959) administered purified anterior pituitary growth hormone to a dog simultaneously with tolbutamide, and obtained similar results. They found that the diabetogenic effect of daily intramuscular injections of somatotrophin is

decreased or inhibited by the concomitant oral administration of tolbutamide. It is probable that a rise in the rate of insulin secretion and an increase in the number of beta cells capable of secreting insulin are concerned in this protective mechanism exerted by the sulphonamides against the development of meta-hypophyseal diabetes.

Recently we have attempted to investigate the possibility of a preventive action of hypoglycæmic sulphonamides against the exhaustive and degenerative process which "spontaneously" occurs in the pancreatic remnant of a subtotally pancreatectomized animal (Loubatières, Fruteau de Laclos, Mariani and Sassine, 1960; Loubatières, Mariani, Fruteau de Laclos and Sassine, 1960). It is well known that the maintenance of about one-tenth of the initial pancreatic gland is able to prevent, for a time, the development of diabetic symptoms. In our experiments dogs, male and female, were operated on and a pancreatic remnant of about one-tenth of the initial gland was left *in situ* around the proximal part of Wirsung's duct. Then, a glucose tolerance test (1 g/kg glucose orally) and a sulphonamide test (25 mg/kg chlorpropamide orally) were performed separately every fifteen days under standard conditions. Between the test days, each animal received a meat diet (15 g of raw horse-meat per kg of body weight twice a day) and 25 mg/kg of chlorpropamide. Chlorpropamide was chosen because of its long-lasting action.

So far, although receiving sulphonamide for ten months, the animals are not diabetics and their glucose tolerance tests are not higher nor more prolonged than before sulphonamide treatment. In fasting conditions their blood sugar was below the normal level. After normal meals it did not exceed 100 mg/100 ml. In the majority of glucose tolerance tests a deep hypoglycæmic trough followed the hyperglycæmic period. In fact, we noticed that the glucose curves were better if sulphonamide was stopped forty-eight hours before the test; a possible explanation of the phenomenon is that sulphonamide treatment relatively reduced insulin reserves already contained in the beta cells.

Our work is still in progress and it is not yet possible to conclude that sulphonamides have a definitive protective action on the beta cells although we are inclined to think so. It is probable that the regenerative and neoformative processes as well as the protective action that sulphonamides exert on the beta cells are largely responsible for the phenomenon we have been describing. This is in agreement with histological studies of pancreatic remnant biopsies.

We must emphasize that maintenance of functionally intact exocrine tissue is necessary for its demonstration (Loubatières, Fruteau de Laclos, Mariani and Sassine, 1960). For example, in the dog the formation of new beta cells, as well as the action of sulphonamides on the insulin-secreting process itself, is largely jeopardized by the progressive sclerosis in the pancreatic graft transplanted to the wall of the abdomen, although circulation in the graft is maintained through its vascular pedicle. It is possible, also, that the hypoglycæmic action of sulphonamides favours the new formation and regenerative action these substances exert on the beta cells. It is evident that the electron microscope will be an important aid to progress in this type of investigation.

We must now ask if this "curative" or "preventive" action of sulphonamides occurs in human diabetes. In certain elderly diabetic subjects, with mild diabetes, it is sometimes possible to observe, after suspension of sulphonamide treatment, a blood-sugar level which is relatively satisfactory and which can be maintained for several weeks or months. After this period of "long-lasting" remission, the blood-sugar level tends to rise progressively and finally the full diabetic condition returns (*see* Loubatières, 1958, 1959*c*, *d*; Bloom, 1959). It must be emphasized, however, that the better the diet is balanced and the more strictly it is followed the longer will equilibrium be maintained, and the longer the remission. A diabetic relapse is probably due to the exhaustion of new beta cells or to the progressive impairment of their membrane permeability to blood glucose on the one hand or to endogenous insulin on the other.

In certain young diabetics, with an undoubtedly familial trait of diabetes, but whose diabetes is of *recent* origin and has not yet resulted in a loss of body weight, treatment with sulphonamide can cause the diabetic symptoms to disappear at least for a time. Whatever the explanation, this phenomenon is important and has been observed by many authors, e.g. Larsson (1959), Otto and Mai (1959).

If we admit that hypoglycæmic sulphonamides are able to provoke or to prolong a remission in the evolution of diabetes, could not these drugs be used as preventive or arresting agents in the course of diabetes? This problem, which I had suggested in 1958 (Loubatières, 1958*b*, *d*), was recently investigated during prolonged experiments (up to twenty-two months) by Fajans and Conn (1960). They studied the effects of sulphonylurea therapy on carbohydrate tolerance of young, non-obese patients with mild, asymptomatic diabetes mellitus, and concluded that (I quote): "(1) Carbohydrate tolerance improved

or became normal in thirteen of fourteen young, non-obese, mild diabetic patients during treatment with tolbutamide over a period of two to twenty-two months. (2) Normalization of the response to a glucose load as well as occurrence of fasting and postprandial hypoglycemia suggest increased insulin secretion as a mode of action of tolbutamide in these patients. (3) The studies reported could have important bearing on the problem of prevention of diabetes mellitus."

More extensive studies are needed to determine whether prolonged treatment with hypoglycæmic sulphonamides can prevent or reduce numerical or functional decompensation of insulin-secreting cells in man as well as in animals. Many authors, notably Gepts (1959), have observed signs of beta cell regeneration and islet hyperplasia in the pancreas of patients submitted to prolonged treatment with sulphonamides.

It is particularly desirable that experiments of the type done by Fajans and Conn should be expanded both in the numbers of patients and in the duration of the observation. Success will depend upon strict control of treatment and diet and careful selection of patients in the early stage of diabetes.

REFERENCES

Ashworth, M. A., and Haist, R. E. (1956) *Canad. med. Ass. J.*, **74,** 975.

Bloom, A. (1959) *Brit. med. J.*, ii, 731.

Brion, A., and Fontaine, M. (1959) *Thérapie*, **13,** 68.

Creutzfeldt, W., and Finter, H. (1956) *Dtsch. med. Wschr.*, **81,** 822.

Fajans, S. S., and Conn, J. W. (1960) *Diabetes*, **9,** 83.

Fruteau de Laclos, C., and Loubatières, A. (1960) *Bull. Ass. Anat., Paris*, No. 106, 261.

Gepts, W. (1959) In: Oberdisse and Jahnke (1959) p. 255.
——, Christophe, J., and Bellens, R. (1955) *Ann. Endocr., Paris*, **16,** 946.
——, ——, —— (1956) *Ann. Endocr., Paris*, **17,** 276.

Holt, C. von, Holt, L. von, and Kröner, B. (1956) *Naturwissenschaften*, **43,** 162.

Houssay, B. A., and Migliorini, R. H. (1956) *C.R. Soc. Biol., Paris*, **150,** 1620.

Jores, J., and Kracht, J. (1959) *Acta endocr., Copenhagen*, **32,** 243.

Kracht, J. (1958) Die Therapie des Monats. Mannheim; 8/9, 250.

Lacy, P. E., and Hartroft, W. S. (1959) *Ann. N.Y. Acad. Sci.*, **82,** 287.

Larsson, Y. (1959) In: Oberdisse and Jahnke (1959) p. 504.

Lever, J. D., and Jeacock, M. (1960) *J. Anat., Lond.*, **94,** 293.

Loubatières, A. (1944) *C.R. Soc. Biol., Paris*, **138,** 766.
—— (1946*a*) *Arch. int. Physiol.*, **54,** 174.
—— (1946*b*) Thèse Doct. Sci. naturelles, Montpellier No. 86.
—— (1955) *Pr. Méd.*, **63,** 1701, 1728.
—— (1957*a*) *Ann. N.Y. Acad. Sci.*, **71,** 192.
—— (1957*b*) *Diabetes*, **6,** 408.
—— (1957*c*) *Ann. Endocr., Paris*, **18,** 161.
—— (1958) *Pr. Méd.*, **66,** 1175, 1229.
—— (1959*a*) XXI *Int. physiol. Congr.*, p. 68 (abstracts).
—— (1959*b*) Conférence du Palais de la Découverte. Paris; Série A, No. 254.
—— (1959*c*) *Acta physiol. latin.-amer.*, **9,** 79.
—— (1959*d*) In: Oberdisse and Jahnke (1959) p. 279.
——, Bouyard, P., and Fruteau de Laclos, C. (1955) *C.R. Acad. Sci., Paris*, **241,** 515.
——, ——, —— (1956) *Le Diabète, Paris*, **4,** 38.
——, ——, ——, and Sassine, A. (1956) *J. physiol., Paris*, **48,** 620.
——, ——, ——, —— (1957) *C.R. Soc. Biol., Paris*, **151,** 2179.
——, ——, ——, ——, and Alric, R. (1956) *C.R. Soc. Biol., Paris*, **150,** 1601.
——, ——, and Sassine, A. (1958) *C.R. Acad. Sci., Paris*, **247,** 1497.
——, ——, ——, and Fruteau de Laclos, C. (1957) *C.R. Soc. Biol., Paris*, **151,** 826.
——, ——, ——, —— (1958) *J. physiol., Paris*, **50,** 383.
——, and Fruteau de Laclos, C. (1958) *C.R. Soc. Biol., Paris*, **152,** 1760.
——, ——, Mariani, M. M., and Sassine, A. (1960) *C.R. Soc. Biol., Paris*, **154,** 173.
——, Mariani, M. M., Fruteau de Laclos, C., and Sassine, A. (1960) *J. physiol., Paris*, **52,** 155.
——, Sassine, A., Fruteau de Laclos, C., and Bouyard, P. (1957) *C.R. Soc. Biol. Paris*, **151,** 957.
——, ——, Mariani, M. M., and Fruteau de Laclos, C. (1960) *C.R. Soc. Biol., Paris*, **154,** 155.

Mirsky, I. A., Diengott, D., and Dolger, H. (1956) *Metabolism*, **5,** 875.
——, Gitelson, S., and Perisutti, G. (1959) *Ann. N.Y. Acad. Sci.*, **74,** 499.

Oberdisse, K., and Jahnke, K., eds. (1959) Diabetes Mellitus. III Kongress der International Diabetes Federation. Stuttgart.

Otto, H., and Mai, K. (1959) In: Oberdisse and Jahnke (1959) p. 512.

Pfeiffer, E. F., Steigerwald, H., Sandritter, W., Bander, A., Becker, M., and Retiene, K. (1957) *Dtsch. med. Wschr.*, **82** (ii), 1568.

Pozza, G., Galansino, G., and Foa, P. (1956) *Proc. Soc. exp. Biol., N.Y.*, **93,** 359.

Volk, B. W., Weisenfeld, S., Lazarus, S. S., and Goldner, M. G. (1956) *Metabolism*, **5,** 894.

Young, F. G. (1956) *Brit. med. J.*, ii, 431.
——, Lever, J. D., and Jeacock, M. (1959) Personal communication.

Dr. John Malins (Birmingham):

It is generally agreed that the sulphonylureas are effective in lowering the blood sugar of some diabetic subjects, that this is an insulin effect and that tolbutamide and chlorpropamide are safe enough to be used in general practice, the side-effects being minimal if the correct dosage is adhered to. With all the sulphonylureas, the effective dose varies little from patient to patient, and if an adequate blood level of the drug is achieved, but without clinical response, nothing is gained by increasing the dose. At the General Hospital, Birmingham, 1,129 patients have received oral treatment—72 with carbutamide, 753 with tolbutamide and 304 with chlorpropamide, which, because of its prolonged action and powerful effect, is now the drug of choice. The combination of sulphonylurea with insulin was abandoned as there was no evidence that it improved control. The diguanides with their unphysiological mode of action are not as yet considered safe for general use.

Oral treatment is considered: (1) In newly diagnosed cases thought unlikely to respond to diet; or when a symptom such as pruritus vulvæ is so severe that rapid removal of glycosuria is essential. (2) When diet has failed either to control symptoms or to keep the blood sugar within the normal range. These patients are often obese and lack the will power to lose weight. It is necessary to decide whether obesity or uncontrolled diabetes is the greater threat to life. If prolonged efforts at dieting have failed (and every patient should have the principles of dieting carefully explained) it is best to treat the hyperglycæmia as such. Patients with a persistently raised blood sugar run an increased risk of complications either acute, such as neuropathy, or chronic and vascular. (3) Those receiving insulin, but whose lives do not seem to depend on it, are considered for oral treatment, particularly if hypoglycæmia is troublesome; hypoglycæmia is the greatest disadvantage of insulin treatment. All patients under the age of 40 and all those who take more than 30 units of insulin daily may be excluded as only a minority in these groups would respond, but the exceptions can be important, e.g. men who have to change their work if put on insulin, and elderly patients living alone. Conversely oral treatment is not always satisfactory for these patients, because they may forget or neglect to take tablets.

To evaluate oral treatment in clinical practice 468 cases of newly diagnosed diabetes who attended in 1958 have been analysed. Table I shows the initial treatment and the results at the end of one year. "Satisfactory" denotes a complete response with a normal blood sugar one hour after a meal. "Partial" denotes relief of symptoms with a blood sugar below 250 mg/100 ml, and "Failure" the persistence of symptoms with a blood sugar above 250 mg/100 ml.

TABLE I.—INITIAL TREATMENT AND THE RESULTS AFTER ONE YEAR

468 PATIENTS

	Diet only	Oral	Insulin
Initial treatment ..	53%	34%	13%
At one year	41%	38%	21%

At one year	Satisfactory	Partial	Failure
Diet only (249 cases)	56%	18%	26%
Oral treatment (157 cases)	48%	25%	27%

Apart from those cases considered mild enough for diet only or severe enough to need immediate insulin therapy, all patients were eligible for oral treatment regardless of age, blood sugar or moderate ketonuria. Two patients were controlled perfectly throughout pregnancy with delivery of healthy infants at the 37th week.

Table II shows the results of oral treatment at the end of one year related to age, body weight, and the initial blood sugar.

TABLE II.—RESULTS OF ORAL TREATMENT AFTER ONE YEAR IN RELATION TO AGE, BODY WEIGHT AND INITIAL BLOOD SUGAR

249 (NEWLY DIAGNOSED) CASES

	No. of patients	Satisfactory	Partial	Failure
Age:				
Under 40	14	38%	8%	54%
40–70	205	51%	24%	25%
70 and over	30	50%	37%	13%
Body weight:				
Thin	16	28%	24%	48%
Normal	85	51%	22%	27%
Fat	148	63%	26%	11%
Initial blood sugar:				
Over 400 mg/100 ml ..	21	37%	20%	43%
300–400 mg/100 ml ..	60	40%	30%	30%
Under 300 mg/100 ml ..	168	60%	24%	16%

It appears that a good response is most likely in those over the age of 40, those who are obese and those with an initial blood sugar below 300 mg/100 ml, but is by no means rare in the other groups. Our experience confirms that of Mehnert *et al.* (1958), that oral treatment is more successful in men than women, in the older patient, and in those with a shorter history of previous treatment, low insulin requirements and short duration of insulin treatment. But these are generalizations and it is worth emphasizing once more that the exceptions form a significant group and one in which a good result may be especially desirable.

REFERENCE

MEHNERT, H., CAMERINI-DAVALOS, R., and MARBLE, A. (1958) *J. Amer. med. Ass.*, **167**, 818.

Dr. J. D. N. Nabarro, Dr. Paul Mestitz and **Dr. J. D. H. Slater** (London):

The hypoglycæmic sulphonamide derivatives have been shown to control diabetes in some middle-aged patients, but the development of "acquired resistance" is a source of anxiety. At the Middlesex Hospital Diabetic Clinic 107 patients responded satisfactorily to tolbutamide when they were started on this form of treatment between two and four years ago. At the present time only 27 remain satisfactorily controlled by the drug, 35 have developed "acquired resistance", 10 have been taken off it on account of side-effects (rashes in 3 and abdominal pain in 7), and 10 because they were putting on too much weight. The time of development of the acquired resistance is shown in Table I.

The rate of development of resistance is approximately 2% of patients on treatment per month; this may be compared to the figure of 3% per month given by DeLawter *et al.* (1959).

TABLE I
Duration of treatment (months)

	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48
Number of patients at the start of the period	107	95	78	55	44	28	9	3
Number becoming resistant in the six-month period ..	2	8	9	6	5	3	1	1

Chlorpropamide has now been on trial for about two years. It is more potent as a hypoglycæmic agent, partly because excretion is slower and the blood levels are higher but in addition it seems to have a greater effect than tolbutamide at the same blood level (Stowers *et al.*, 1959). The increased potency is shown in Fig. 1. The patient became resistant to 3 g per day tolbutamide after two years' treatment. When this drug was stopped the blood sugar rose by 100 mg/100 ml. Chlorpropamide treatment was started and after some adjustment of the dose satisfactory control was obtained with 0·5 g/day with reduction of blood sugar by 200 mg/100 ml. The patient has now remained well controlled on chlorpropamide for twelve months.

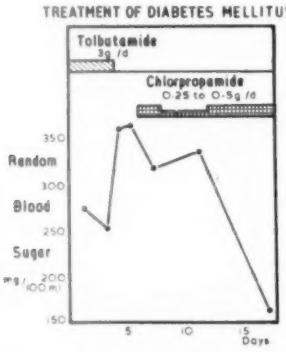

FIG. 1.—R. K., female, aged 46. Diabetes eight years. 15% below average weight. Diet 120 g CHO. Tolbutamide treatment two years.

The results of giving chlorpropamide to patients with acquired resistance to tolbutamide confirm that it is a more potent hypoglycæmic agent. Of 25 patients so treated, 15 have been well controlled for periods of up to eighteen months, 7 failed to respond and 3 after an initial response have developed acquired resistance to chlorpropamide.

When chlorpropamide was first introduced the doses used were excessive, and troublesome side-effects like drowsiness, confusion and ataxy were noted (Murray *et al.*, 1958). A number of patients developed cholangiolitic hepatitis (Brown *et al.*, 1959). These complications are unusual with the dose currently employed. We have given chlorpropamide to 95 patients, and the doses used for maintenance therapy have been from 100 to 500 mg/day. Side-effects noted have been mild abdominal discomfort (2 patients) and in 2 others skin rashes have necessitated stopping treatment. One patient has had hypoglycæmic attacks. Acquired resistance to chlorpropamide has developed in 6 patients: 3 transferred from tolbutamide, having become resistant to that drug, became resistant to chlorpropamide after six to eleven months' treatment and 3 treated only with chlorpropamide developed resistance after eight to fifteen months. These 6 cases of acquired resistance have developed in a group of 81 giving an initial satisfactory response; at a comparable stage in our tolbutamide trial the incidence was 12 out of 79.

Patients who have failed to respond to chlorpropamide or who have become resistant to its action are now being given small doses of diguanides in addition. Of 6 primary failures, 4 have responded to this combination of hypoglycæmic agents. 3 cases of acquired resistance have been given phenformin or metformin with the chlorpropamide and all are at present satisfactorily controlled.

REFERENCES

BROWN, G., ZOIDIS, J., and SPRING, M. (1959) *J. Amer. med. Ass.*, **170**, 2085.

DELAWTER, D. E., MOSS, J. M., TYROLER, S., and CANARY, J. J. (1959) *J. Amer. med. Ass.*, **171**, 1786.

MURRAY, I., RIDDELL, M. J., and WANG, I. (1958) *Lancet*, ii, 553.

STOWERS, J. M., CONSTABLE, L. W., and HUNTER, R. B. (1959) *Ann. N.Y. Acad. Med.*, **74**, 689.

Dr. R. S. Walker (Glasgow):

Phenethyldiguanide (D.B.I.)

Phenethyldiguanide (D.B.I.) is a potent hypoglycæmic drug, whether or not there is an intrinsic source of insulin: accordingly it has been claimed to have a place in the treatment of all types of diabetes (Steiner and Williams, 1959; Pomeranze *et al.*, 1959). This paper is a report of our experiences with 109 patients in two years. The cases were selected only on their need for inception of therapy or alteration of existing treatment and on their ability to co-operate.

The patients were divided, before treatment began, into four somewhat arbitrary groups: (1) Adult (stable): Appearing after 40 without initial ketonuria. Low insulin dose <40 units. (2) Juvenile (unstable): Acute onset, ketonuria. (3) Stable juvenile: No history of ketosis. Low insulin dosage, slow onset. (4) Unstable adult: Acute onset with ketosis, age over 40.

The grouping of the 109 patients and the success rates in the various groups are shown in Table I.

TABLE I

	No. of patients	Successes	Partial successes	Failures
Adult (stable) ..	48 (44%)	28 (58%)	5 (11%)	15 (31%)
Juvenile (unstable) ..	37 (34%)	—	11	9 early, 17 late
Stable juvenile ..	17 (16%)	6	2	9
Unstable adult ..	7 (6%)	1	2	4
Total	109	35 (32%)	20 (18%)	54 (50%)

Partial success indicates that the insulin dose was less than two-thirds of the initial one and control was better as measured by blood-sugar levels and absence of hypoglycæmia.

The third and fourth groups behave like the major divisions. The adult unstable resembled the juvenile unstable, and the two stable groups were similar.

The success rate of adult cases was further analysed in relation to previous therapy: dietary cases, 83% success; previous insulin therapy, 22% success; failed oral drug, 66% success. The successes were for a mean of 15⅓ months. The appearance of secondary failures was unusual but did occur. However, the drug compares favourably with the sulphonylureas in the new adult case.

The causes of early and late failure are shown in Table II. Nausea rarely led to failure when the drug was only increased slowly; in adults it appeared later in 6 cases after an average of almost six months. Secondary or late failure of hypoglycæmic effect occurred in

TABLE II.—CAUSES OF FAILURE

	Adult	Juvenile	Stable juvenile	Unstable adult
Early:				
No hypoglycæmic effect	5	5	1	2
Nausea	—	3	2	—
Ketosis	—	1	—	—
Late:				
Ketosis	3	8	—	1
Secondary failure	1	7	2	1
Nausea	6	2	4	—

the three larger groups, and was more frequent in the insulin-dependent. Ketosis occurred fairly frequently, sometimes with normoglycæmia, and the drug had to be withdrawn (Hall *et al.*, 1958). Primary failure of hypoglycæmic effect occurred fairly often in insulin-dependent patients, but did not occur in a "new" case.

Examples of secondary failure were: (1) An adult who had twelve months' good control of blood sugar after which the levels were unaltered by increased dosage. (2) A juvenile case, controlled well for fifteen months and previously reported, I think justifiably, as a success. She later failed, in spite of increased dose. When supplementary insulin control was established and the drug withdrawn, no effect was noted on the insulin requirement. (3) A juvenile case temporarily well controlled but the hypoglycæmic effect failed after four months. Reintroduction of D.B.I. had no effect on insulin needs.

The appearance of acetonuria with normal or mildly elevated blood sugars has caused us much anxiety. This is a phenomenon peculiar, so far as we know, to this drug. It has been associated with very low alkali reserve and in 2 cases the levels were 3·0 and 4·9 mEq/l. with blood sugars of 270 and 210 mg/100 ml (Walker and Linton, 1959). The former patient died, although on a supplement of 12 units of insulin, after nine months of adequate control. These two were extreme examples of a trend we encountered often. Of 35 who showed ketonuria, only 9 were adult. Of the 11 severely acidotic, as measured from the alkali reserve, only 1 was an apparently stable adult.

The keto-acidosis picture appeared more often after sustained exercise and for this reason we tried exposing normals, diabetics on insulin and diabetics on D.B.I. to standard exercise. Lactic acid levels were estimated immediately and fifteen minutes later; the results indicate that these are severely disturbed (*see* Fig. 1).

Moreover, many resting blood lactate levels were considerably elevated. This we regard as evidence that in the unstable and presumably insulin-dependent diabetic, a disturbance of

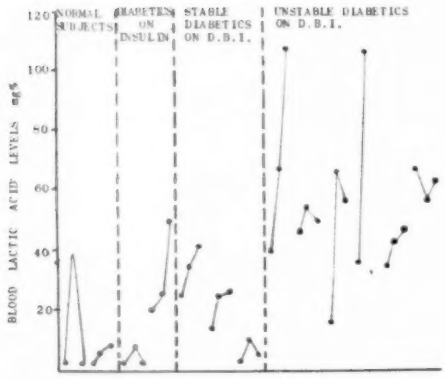

FIG. 1.—Blood lactic acid levels before and after standard exercise and fifteen minutes later. Note higher initial levels and greater rise shown by unstable diabetics on D.B.I.

carbohydrate metabolism exists so that lactate disposal is impaired or excess production occurs (Moorhouse *et al.*, 1958). As several of these patients were on supplementary insulin, it is possible that D.B.I. can alter its action.

The patients were under the care of Dr. A. C. Aitkenhead; Dr. W. S. T. Thompson, Dr. A. L. Linton and Dr. R. Hannah have assisted in much of this work.

REFERENCES

HALL, G. H., CROWLEY, M. F., and BLOOM, A. (1958) *Brit. med. J.*, ii, 71.

MOORHOUSE, J. A., FAJANS, S. S., and CONN, J. W. (1958) *Clin. Res.*, **6**, 405.

POMERANZE, J., MOURATOFF, G. T., GADEK, R. J., and KING, E. J. (1959) *J. Amer. med. Ass.*, **171**, 252.

STEINER, D. F., and WILLIAMS, R. H. (1959) *Diabetes*, **8**, 154.

WALKER, R. S., and LINTON, A. L. (1959) *Brit. med. J.*, ii, 405.

Dr. J. M. Stowers (St. Andrew's University):

The Value of Phenformin in the Treatment of Unstable Diabetes [*Summary*]

Many authors have claimed that phenformin (D.B.I.) can notably stabilize brittle diabetics, when used in conjunction with reduced doses of insulin to avoid ketosis, but this contention has never been proved by objective data subjected to statistical analysis. This paper presented such data and analyses obtained from 9 typical brittle diabetics studied as hospital in-patients. They were on a regime of constant exercise and diet, and the capillary blood sugar was measured in duplicate at 8 a.m. (fasting), 1 p.m. (one hour after lunch) and 8 p.m. (two hours after high tea). The daily excretion of sugar was also measured. In the control period these data were obtained while the patients were having what was considered to be their optimal diet and dose of insulin. In the test period these measurements were continued while the patient had phenformin 25 mg q.i.d. and an appropriately reduced constant dose of insulin. The standard deviation of the blood sugar was calculated for each of the three times during the control and test periods (the inter-diem variations) and the standard deviation of the blood sugar was calculated during each day for the control and test periods (the intra-diem variations). None of the apparent differences in the standard deviations between the control and test periods was shown to be statistically significant (Student's *t* test), but there was little doubt that these patients experienced fewer hypoglycæmic symptoms at comparable levels of control when taking phenformin plus a reduced dose of insulin. This proved clinically to be a worth-while advantage in several patients on prolonged out-patient treatment. Phenformin does not produce hypoglycæmia in non-diabetic individuals (Skillman *et al.*, 1958), nor is it prone to do so in diabetics when used alone (Odell *et al.*, 1958). Krall *et al.* (1958) have noted the resistance of diabetics taking phenformin to the development of hypoglycæmic symptoms, even when the blood sugar has been as low as 18, 23 and 25 mg/100 ml. This suggests that phenformin increases the permeability of the cells to glucose.

3 of the 20 patients so far treated with phenformin have developed œdema which may be related to the phenformin. Detailed data were presented on one patient who showed a considerable reduction in his response to two diuretic regimes while he was taking phenformin, although the latter could not be held responsible for the œdema in this case.

Acknowledgment is made to Dr. W. T. Strauss for clinical, and to Dr. F. L. Mitchell and Miss L. W. Constable for biochemical assistance, to the house physicians and ward sisters for careful withdrawal of duplicate capillary blood specimens and to Dr. Boheimer of Bayers Ltd., for supplies of phenformin.

REFERENCES

KRALL, L. P., WHITE, P., and BRADLEY, R. F. (1958) *Diabetes*, **7**, 468.

ODELL, W. D., TANNER, D. C., STEINER, D. F., and WILLIAMS, R. H. (1958) *Arch. intern. Med.*, **102**, 520.

SKILLMAN, T. G., KRUGER, F. A., PETERSON, L. G., and HAMWI, G. J. (1958) *Clin. Res.*, **6**, 253.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Albot (G.), and **Poilleux (F.).** La maladie lithiasique des voies biliaires. La lithiase vésiculaire. pp. 341. Paris: Masson. 1959.

Bowesman (C.). Surgery and clinical pathology in the tropics. pp. 1068. Edinburgh and London: Livingstone. £5 10s. 1960.

British National Formulary, 1960. Standard edition. pp. 172. London: B.M.A. and Pharmaceutical Society. 7s. 6d. 1960.

Cacace (E.), ed. Trattato di nipiologia. 2 vols. Torino: Edizioni Minerva Medica. 1958–1959.

Congresses, Occupational therapy. Occupational therapy as a link in rehabilitation. Proceedings of the II International Congress of the World Federation of Occupational Therapists, held at Copenhagen August 11–16, 1958. pp. 326. Århus. 1959.

Davies (P. M.). Medical terminology for radiographers. pp. 242. London: Heinemann. 15s. 1960.

Eşanu (G.), and **Banc (S.).** Substituentii macromoleculari de volum ai plasmei. (Biblioteca medicala XX.) pp. 227. Bucuresti: Editura Academiei Republicii Populare Romine. 1959.

Falcão (E. de C.). Piraja da Silva: o incontestavel descobridor do "Schistosoma Mansoni". pp. 314. São Paulo. 1959.

Finlay (C. J.). Dr. Carlos J. Finlay and the "Hall of Fame" of New York. pp. 141. Havana: Ministry of Health and Hospital's Assistance. 1959.

Fonseca (A. F. da). Análise heredo-clínica das perturbaçðes afectivas. (Estudo de 60 pares de gemeos e seus consanguineos.) pp. 282. Porto: Imprensa Portuguesa. 1959.

Forsyth (G.), and **Logan (R. F. L.).** The demand for medical care: a study of the case-load in the Barrow and Furness Group of Hospitals. (Nuffield Provincial Hospitals Trust.) pp. 153. London: O.U.P. 7s. 6d. 1960.

Frankel (V. H.). The femoral neck: an experimental study of function, fracture mechanism, and internal fixation. pp. 114. Uppsala: Almqvist and Wiksells. 1960.

Gonzalez Marmol (D.). La endometriosis. pp. 359. La Habana: Roger A. Queralt. 1959.

Grumbach (A.), and **Kikuth (W.).** Die Infektionskrankheiten des Menschen und ihre Erreger. 2 Bde. pp. 1702. Stuttgart: Thieme. DM 198. 1958.

Guirdham (A.). Man: divine or social. pp. 230. London: Stuart. 27s. 6d. 1960.

Hoeppli (R.). Parasites and parasitic infections in early medicine and science. pp. 526. Singapore: University of Malaya Press. M$ 25 (£3 3s.). 1959.

I Jugoslovenski Simpozijum o Gušavosti, Beograd, 9–11 XII 1957 Godine. pp. 342. Beograd: Komisja za Medicinsko-Naučna Istrazivanja. 1959.

Kelemen (E.). Permeability in acute experimental inflammatory œdema. pp. 256. Budapest: Publishing House Hungarian Academy of Sciences. 1960.

Lenzi (E.). L'ernia vaginale del Douglas o elitrocele. pp. 137. Pisa: Edizioni "Omnia Medica". 1959.

Lewison (L.). You and your eyes. pp. 253. New York: Trinity Publishing Corporation. $3.50. 1960.

Liddell (E. G. T.). The discovery of reflexes. pp. 174. Oxford: Clarendon Press. 30s. 1960.

Macfarlane (L. R. S.). A short synopsis of human protozoology and helminthology. pp. 251. Edinburgh and London: Livingstone. 35s. 1960.

Mason (A. A.). Hypnotism for medical and dental practitioners. pp. 223. London: Secker and Warburg. 30s. 1960.

Neubauer (O.). Bibliography of cancer produced by pure chemical compounds. pp. 604. London: O.U.P. 42s. 1959.

Nicolesco (J.). Travaux scientifiques. pp. 617. Bucarest: Editions de l'Academie de la Republique populaire Roumaine. Paris: Masson. 1959.

Speedby (H. J.). The 20th century and your heart. pp. 192. London: Centaur Press. 18s. 1960.

Williams (E. L.). Tomorrow will be sober. pp. 208. London: Cassell. 15s. 1960.

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Meeting
March 3, 1960

MEETING HELD AT THE MAIDA VALE HOSPITAL FOR NERVOUS DISEASES, LONDON

THE following cases were shown:

Two Cases of Tremor in Disseminated Sclerosis treated by Chemothalamectomy.—Dr. H. DIMSDALE and Mr. A. M. H. BENNETT.

Blastomatous Sclerosis.—Dr. B. COOPER and Dr. S. NEVIN.

Two Cases of Myxœdema with Muscular Pseudohypertrophy.—Dr. E. H. JELLINEK (for Dr. R. E. KELLY and Dr. J. MARSHALL).

Claudication as a Symptom of Brain-stem Ischæmia.—Dr. G. STERN (for Dr. J. MARSHALL).

Isolated Paralysis of Conjugate Lateral Gaze.—Dr. B. MACGILLIVRAY (for Dr. S. NEVIN).

Intracranial Calcification ? Healed Meningeal Tuberculosis.—Dr. R. E. KELLY.

Meeting
May 5, 1960

THE HISTORY OF NEUROLOGY

Neurological Investigation in Britain from 1800 to the Founding of The National Hospital

By W. H. MCMENEMEY, M.D.

London

IN this centenary year we meet to honour the memory of those who founded The National Hospital for Epilepsy and Paralysis, the history of which has already been faithfully recorded by Sir Gordon Holmes.

The first aim of the founders was to segregate and care for the poor afflicted with two socially unpopular diseases but there is little doubt that they wished also to establish a centre for clinical research. Marshall Hall, the leading neurologist in mid-nineteenth century Britain, did not live to see this hospital founded but he had in mind the likely benefits which would accrue from careful observation of these patients in life and of their bodies after death. So impressed was he with the alleged beneficial effects of tracheostomy in controlling the spasms of epileptics (a treatment attributed by Brown-Séquard to Hall) that we find him in 1852, ten years before Charcot began his reorganization of the Hospice de la Salpêtrière, advocating that such a hospital should be founded, although some years previously he had reluctantly come to the conclusion that the scheme was impracticable on the grounds that it would be too distressing for epileptics to witness the convulsions of their fellow sufferers.

Medical progress is determined essentially by individual effort and opportunity, both chance and created, but also by communication through the media of meetings and the printed word. In the nineteenth century improved facility of travel and particularly the advent of the railways encouraged the former and the growth of medical journalism did much to help the dissemination of the latter. The century in fact began well with the appearance in 1805 of the *Edinburgh Medical and Surgical Journal*, a laudable design to link together the medical metropolises of Edinburgh and London. War and revolution facilitate the exchange of ideas, throwing allies together and bringing in colleagues and refugees with different medical upbringing, discipline and outlook. During the early part of the period under review Britain was embarrassed by the Napoleonic wars but the influence of the French revolution and the intellectual renaissance which followed was felt in British medicine as in politics and literature well into the century. Except in Edinburgh and Glasgow medicine as an art and science in British universities hardly existed, but the private anatomical academies and the embryonic schools attached to some of the London and provincial hospitals acted as minor centres of learning while the Medical Society of London and this Medical and Chirurgical Society served as important focal points for the pooling

of knowledge. The Royal Society was the principal forum for debating scientists amongst whom the leading physicians and surgeons of the day figured prominently.

The early nineteenth century neurologist appears to have derived his academic inspiration in part from the Collège de France and the Académie des Sciences and in part from the University of Edinburgh. From William Cullen, Robert Whytt and Alexander Monro *secundus*, whose outlook probably owed more to the teachings of Franz De Le Boë and Boerhaave than to those of Harvey and Willis, he inherited a fine tradition. As a science, however, neurology was scarcely in being and this in spite of the fact that there was in the first quarter of the century a keen interest in physiology stemming especially from the work of Dumas, Bichat, Desmoulins and Legallois. Treatment was still largely empirical and in nosology there was too much conjecture, to curb which laboratory and bedside techniques were at too immature a stage of development. In 1821 Charles Bell wrote: "The endless confusion of the subject induces the physician . . . to dismiss it from his course of study as a subject presenting too great irregularity for legitimate investigation or reliance."

The challenge was taken up by Romberg (1840) and, as we know, his attempt to classify diseases of the nervous system was commendable. We may take just pride in the knowledge that this pioneer of academic neurology admitted that it was in the works of English (and I suppose he meant British) authors that he found instruction. He was familiar not only with the writings of Bell but also with those of Cheyne (1812), John Cooke (1820–1823) and Abercrombie (1828). He claimed to have been first attracted to neurology when he translated Andrew Marshal's "The Morbid Anatomy of the Brain in Mania and Hydrophobia" (1815), a too little known work which reveals in a striking way the helplessness of the investigator who had no access to a microscope and possessed, it would seem, no inkling as to its potentialities. Yet this was one hundred and thirty-nine years after van Leeuwenhoek had seen and illustrated bacteria and spermatozoa. In the absence of tumours or ramollissements in the brain the pathologist of Napoleon's day could record only the size of the ventricles, the character of the liquid inside them, the delicacy or coarseness of the leptominges and the consistence of the unfixed and doubtless often decomposed brain. Many of our most competent observers were content with careful clinical descriptions, perhaps in the knowledge that no abnormality would be detectable at necropsy. John Badham's admirable account (1835) of 4 cases of infantile paralysis met with in his practice in Worksop is unsupported by post-mortem findings (it antedated Jacob von Heine's monograph by four years). James Parkinson (1817), however, was thinking along both anatomical and physiological lines when he bade the pathologists of the future to seek out the cause of "the shaking palsy" in "the superior part of the medulla spinalis". He imagined that the tremor might be related to a local increase of blood supply occasioned perhaps by trauma and he prophesied that no abnormality would be found in the encephalon.

Romberg was not alone in attempting to make good the deficiency mentioned by Bell for Marshall Hall published his "Lectures on the Nervous System and its Diseases" in 1836. The German work is of course more in the nature of a textbook, whereas Hall's embodies an attempt at systematic classification on a background of his own physiological researches and hypotheses. Both owed much to John Abercrombie whose "Pathological and Practical Researches on Disease of the Brain and Spinal Cord" (1828) is so well set out, systematically arranged and is so full of interesting clinical case histories with post-mortem reports: with all due modesty he apologized for obtruding his views upon the profession, to do which, he said, for a physician must always be a "matter of the utmost delicacy".

Foremost amongst the morbid anatomists of the early years of the century was Matthew Baillie. The neurological contributions to his illustrated book, the two editions of which were published in 1799 and 1812 respectively, are, however, disappointing, being few in number and almost devoid of clinical information: the specimens he illustrates were mostly from the museum of the Hunters. One is a left frontal lobe abscess and the brain has been cut in the coronal plane as is our usual practice to-day.

In 1826 there appeared Richard Hooper's "The Morbid Anatomy of the Human Brain", but the specimens he portrays again lack adequate clinical data. The encysted tumour on p. 33 is probably an old-standing abscess and those on p. 34 hydatids, for Sir Anthony Carlisle, he tells us, had seen such cysts in the human brain and Dr. Monro also knew about them. (So too did Dr. Abercrombie!) Hooper noted that on putting the cyst contents into alcohol there was much coagulation.

The most important neuropathological contributions of this time are to be found in Richard Bright's case reports (1831) which with their full and instructive clinical histories and protocols are in the true tradition of Benivieni and Morgagni. Case 144 was, it appears, an abscess metatastic from a subphrenic collection of pus. Case 125 was a subarachnoid hæmorrhage in a 19-year-old boy who had suddenly shouted out "Oh, my head". Bright had no difficulty in finding the offending aneurysm in the midst of the blood clot. Case 83 provides a worth-while exercise in diagnosis and a beautiful drawing.

Robert Carswell, first holder of the chair of morbid anatomy at University College, after spending three years in the anatomical museums of Paris, published his "Illustrations of the Elementary Forms of Disease" in 1838, and in fasciculus 10 he has depicted several well-known neurological conditions which have been commented upon by Courville (1948). There is convolutional atrophy to be seen in the brain of a general paretic, more marked on the left side, while under the heading of a "peculiar diseased state of the chord and pons accompanied with atrophy of the discoloured portions" there is a striking illustration of the findings in multiple sclerosis. It is of interest to recall that Cruveilhier also illustrated this disease in the second volume of his atlas (1835–42). Frerichs gave his account of the gross pathology in 1849 and Charcot described his classical "triad" in the year 1868 associating the clinical picture with the anatomical findings already described and so skilfully illustrated. Neither Carswell nor Cruveilhier had quite the same feeling for careful clinicopathological correlation as had the Italian masters, but had Bright been fortunate enough to have dissected a case of this disease it is, I believe, certain that he would not have overlooked its clinical significance. In Carswell's defence, however, it must be added that he had not seen this patient in life and that he had not been able to obtain any distinctive history either of this case or of another whose cord he had also had the opportunity to examine. So-named Rich foci—and let us allow a certain amount of artistic licence—are shown in the brain of a scrofulous person while Carswell illustrates very prettily the effects of circulatory obstruction in the vertebral-basilar system in a case of softening of the pons from which it is clear that he had some knowledge of collateral circulation. This talented artist abandoned his chair of pathology in the year 1840 to become personal physician to the King of the Belgians, but he must have returned periodically to this country for we read[1] that in July 1855 Sir Robert "the eminent pathologist has had the honour of dining with Her Majesty several times during the month".

Thanks largely to the influence of Matthew Baillie, the profession was becoming morbid anatomy conscious, and when Rokitansky visited England in 1842 he was duly impressed, although it is clear that he thought the French were still more praiseworthy. Baillie, Hooper, Bright and Carswell—the observant and artistic morbid anatomists of the first half of the century—did much to acquaint practitioners, or rather those few of them who had access to libraries, of the consequences of focal lesions especially within the confines of the skull. A scrofulous or a scirrhous mass could only be there at the expense of the brain tissue which was being compressed or destroyed. However, they had singularly little idea of the nature of disease and only a rudimentary knowledge of neuro-anatomy, scant progress having been made since the time of von Haller, Prochaska and Monro *secundus*. Their concept of infection was but little removed from that of Fracastoro or of Jean Fernel, for the pioneer views of Bassi on muscardine (1835) had not been generally noted. They awaited the advent of the modern microscope.

In spite of this shortcoming there are several good anatomical studies of this period but few of them are illustrated. Naturally they had to do with the more spectacular lesions such as absence of the corpus callosum (Paget, 1846; Ogier Ward, 1846), cerebral hemiatrophy, encephalocele and hydrocephalus, the common association of which with spina bifida seems to have been generally known. The syndrome of acute hydrocephalus with pulmonary phthisis originally noted by Whytt was by now well recognized (Abercrombie, 1828; Hennis Green, 1835–6; Lumsden, 1841). Wishart's admirable description of multiple tumours of the dura mater and of the nerve roots (1822) deserves to be better known and so long as eponyms remain in use this is one which could justifiably be adopted. There is too the succinct clinicopathological account by Edward Selleck Hare (1838) of the syndrome of paralysis of the cervical sympathetic. He was only 26 years old when, in the same year, he died of typhus contracted in the Staffordshire General Infirmary (Fulton, 1929).

During the 'thirties and 'forties there were physicians in plenty with a competent knowledge of neurology, amongst whom we may mention Henry Clutterbuck, Adair Crawford, Andrew Crawford, Jones Quain, Charles Locock, Harry William Carter, William Bruce Joy, Benjamin

[1] *Lancet* (1855) ii, 43.

Phillips and Robert Bentley Todd. They had had the benefit of training in the post-mortem room which in those days was the hallmark of a good physician, although William Farr (1837) deplored the fact that in pathology we were behind the French. This he attributed to the difficulty of obtaining permission for post-mortem examinations and he blamed the Government: they were apathetic, he said, and slow to appreciate the association between the progress of medicine and the public welfare.

The shelving of the microscope, which had been employed with such promise in the seventeenth century by van Leeuwenhoek, Malpighi and Swammerdam, has been attributed (Guthrie, 1921) to the influence of Stahl, with whose philosophy of animism there went a defeatist attitude concerning the ultimate elucidation of biological phenomena. A more likely explanation is that the possible value of the microscope in medicine had been overlooked throughout a century which belonged more to empiricists than to seekers after truth. Some, however, had been aware of its likely importance but had awaited technical developments.

Monro, an early microscopist of the nervous system, had been alive to the risk of optical deception (1783) and Everard Home (1799), when he studied the optic nerve of a recently-killed horse, noted that with a simple microscope at a magnification of 23 visibility was clear but with a double lens system at 40 the image was indistinct, this being not entirely due to the softness and density of the opaque fibres and to the transparent interstices which he had seen. Nevertheless, he was able to discount the then current view that nerves were hollow tubes but he evidently shared Mr. Ramsden's distrust of the compound microscope.

The compound achromatic microscope (of which Ploessl's was apparently the first) did not make its appearance until the early 'thirties and it took several years before reliable instruments became generally available in this country. Nevertheless it was during this decade that so many pioneer studies were made on the minute anatomy of the brain especially in the schools of Purkinje and Müller. Doubtless Romberg had these in mind when he referred to the "rich treasury of materials" accumulated in that decade.

In the 'forties, however, medical microscopy came very much into fashion in England and at the same time we see also the real beginnings of clinical chemistry. Sir Thomas Watson (1845), writing in the year after Bassi had asserted that contagious diseases were conveyed by living organisms, had little doubt that "animal poisons" effected changes in the blood and were themselves abundantly multiplied or reproduced. The old-fashioned humoral pathology which had sunk into universal discredit was, he told them, back again, but this time as a scientific truth founded on the secure basis of organic chemistry.

"One of the marked features of medical science in the present day," claimed a leader writer[1] in 1846, "is the desire to extend and cultivate our knowledge of pathology. Chemical research and the microscope are earnestly devoted to the subject." But the study of tissues lagged behind that of cells, the difficulties being partly technical. The state of histological fixation prior to the introduction in 1833 of chromic acid by J. Jacobson (Hughes, 1959) must indeed have been primitive for in 1828 Davy advised the burning of sulphur matches over water, the latter being agitated so as to impregnate it with the fumes: he clearly regarded this form of fixative to be as satisfactory as the then conventional spirits of wine.

However, in spite of the many technical difficulties James Paget (1850), as a result of his observations, was able to discuss the role of fatty degeneration of small blood vessels in the causation of apoplexy. Swan (1850) studied the difference between white and grey matter and J. A. Lockhart Clarke (1851), the Pimlico general practitioner, perfected his pioneer anatomical studies on the spinal cord, thin slices of which were clarified in a mixture of one part of vinegar to three of spirits of wine and examined under a Ross microscope. Meanwhile microscopes continued to improve, cytological and nuclear details were revealed, thanks in part to the carmine wash (hæmatoxylin was not introduced until 1863 by Waldeyer), and in the years 1850–2 von Kölliker published the first textbook on histology.

The problem for the early morbid histologist was to appreciate the significance of his findings, a difficulty which we may venture to suggest is being experienced just a century later by the electron-microscopists. However, Luschka's microscopical description of the pacchionian bodies in 1853 was noted[2] with interest and with the publication of William Gull's important series of cases of paraplegia the neurologist realized that he had in microscopic anatomy an additional tool for the investigation of disease. Being a Guy's man and an admirer of Richard Bright, Gull was naturally interested in clinico-pathological correlation. Describing in the year 1856 what was evidently a meningioma he claimed

[1] *Lond. med. Gaz.* (1846) **38**, 83.

[2] *Brit. med. J.* (1853) i, 18.

that it was histologically benign. In another case of intradural tumour resembling, both in appearance and consistence, the infantile testis he speaks of "cohering nuclei, generally oval, but in the firmer parts linear with a small amount of intervening granular blastema which in parts had become incorporated with the nuclei into an obscurely fibrous structure".

In the second series published in 1858 Gull had prepared sections of a spinal cord, after a modification of Lockhart Clarke's method, which showed rather acute posterior-column degeneration. He illustrates clearly the oil drops adherent to the outside of vessel walls seemingly otherwise normal. The incrustation of vessels by this oil, which he could remove by ether, was, he thought, clearly mechanical and not due to degeneration. The patient was a 34-year-old man of dissolute habits and Gull opined that no cause was more efficient in the production of disease of such nature than the contamination of "the syphilitic virus".

Gull's earlier studies appear to have been made on teased fresh specimens, a method in common use in the early days of the compound achromatic microscope. One cannot but admire the work of pioneers like Purkinje, Schwann, Remak, Burdach, Gerlach and in this country Waller, than which nothing more beautiful was to be seen until the usage by Golgi, Cajal and Ford Robertson of metallic impregnation, and one wonders if, had the successors of these experts in microdissection developed along their lines instead of adopting the paraffin block, important contributions in exfoliative cytology, tissue culture and histochemistry need have been so long delayed.

Virchow's "Cellular Pathology", which may be taken to mark the coming of age of histology as a science, was published just two years before the opening of The National Hospital. Thanks to him the neurological world was now able to visualize the neuroglia as well as the nerve cells and he had told them that he believed some of these interstitial cells might be phagocytic in character, thus anticipating the pioneer studies of Ford Robertson and del Rio Hortega.

"A sound physiology must ever go before a sound pathology" Charles Bland Radcliffe once wrote (1858). Throughout the nineteenth century British neurologists, inspired initially by the French school, and expecially it would seem by the publication in 1812 of Legallois's "Expériences sur le Principe de la Vie", remained physiologically-minded, for which fact we can thank the Royal Society who diligently prosecuted this science. It was in Burlington House in the year 1822 that Wilson Philip argued with Benjamin Brodie and Samuel Broughton on the functions of the pneumogastric nerve.

Charles Bell, in a monograph distributed to his friends in the year 1811, asserted that stimulation of the ventral nerve roots of the spinal cord provoked movements, an ability not shared by the dorsal roots. It seems certain from a paper he published in 1821 that he was aware of the fact that stimulation of the exposed trigeminal nerve of an ass evoked acute pain but it appears that he never fully appreciated the significance of his discovery (Gordon-Taylor and Walls, 1958). It was left to the brilliant Magendie to provide by experiment that proof which was still needed to show that roots associated with ganglia have a sensory function. We have recently been reminded (Gordon-Taylor and Walls, 1958) that Bell was investigating sensory pathways "from the outward senses" as early as December 1807 at a time when he was intrigued with the "five tubercles within the brain". Although he never went so far as to agree with Gall on the question of localization of specific functions within the brain—probably because he did not approve of phrenology—he realized in 1811 that the cerebrum had both a motor and a sensory function. He went astray, say Gordon-Taylor and Walls, when he attempted to link them exclusively with the anterior columns and roots and the cerebellum with the posterior columns and roots. However, it was a natural assumption to make. Had he been less meticulous and not so conscientiously averse to animal experimentation and had he not been preoccupied with his professional life as a surgeon he might have pursued his researches at Great Windmill Street more speedily and himself supplied the proof which he left for Magendie. Bell's conduct following the reporting of Magendie's experiments has often been called in question (most recently by Brazier, 1959) but it is generally agreed that the latter owed much to the former who for so many years had pondered these problems. The acrimonious dispute which for long clouded the pages of medical history as to which of the two should claim priority for the enunciation of the "Bell-Magendie Law" is sufficient proof that it was an epoch-making discovery. "The Nervous system" wrote Bell (1821) "hitherto the most unsatisfactory part of a physiologist's studies, has assumed a new character". Bell's work paved the way for others—for Magendie, Marshall Hall and Brown-Séquard in particular—and it led naturally to Müller's Law of the Specific Energies

although, as Riese reminds us, Müller probably also owed much to Gall. Riese (1959) has called Bell "one of the last and most eminent representatives of a purely observational neurology". For the discerning Professor Romberg in Berlin he was the Harvey of the nineteenth century.

Bell was less concerned than others with the much disputed nature of the nervous impulse, the *succus nerveus* of Borelli and the *vis nervosa* of Prochaska and of von Haller. Monro (1783) had been non-committal over its possible identity with the electric fluid but Wilson Philip in 1815 was dogmatic that they were the same as indeed appears to have been the view of John Wesley (1759). This problem, however, was never regarded as settled in the first half of last century. The "electrical virtue", however, had been used therapeutically ever since Lizzie Foster had been cured of her paralysis (Brydone, 1757) by repeated touches of the suspended gun barrel, a fact certified by the Minister of Coldingham, who happened to be the father of the experimenter, as well as by the overjoyed patient herself.

Marshall Hall was 36 years old when in the year 1826 he moved from Nottingham to establish himself in London. He held no regular teaching hospital appointment, and his experiments perforce were mainly carried out at home as a spare-time activity. As a student at Edinburgh he had set time aside each day to read the works of Corvisart, Chardel, Pinel and Bichat, and being a firm admirer of Legallois it is not surprising that he showed an early and sustained interest in neurophysiology. He is credited with the discovery of the reflex arc although the phenomenon of reflex activity was, as we know, familiar to Whytt, Thomas Willis, Descartes and others besides (Hoff and Kellaway, 1952; Green, 1958). It was while observing the activities of a decapitated triton that Marshall Hall suddenly appreciated the biological significance of the spinal cord. He reported his findings to the Zoological Society in 1832 and in the following year wrote his monograph "On the Reflex Function of the Medulla Oblongata and Medulla Spinalis" (Hall, 1833). The recognition of the reflex arc had revealed to him, he said "a totally new order of facts" leading to "a new division of diseases of the Nervous System". Although he was accused of borrowing without acknowledgment from Müller and Prochaska, his was an important discovery but it was the natural sequel of the experiments of Legallois, of Bell, and of Magendie. Flourens with his experiments, said Hall, had located in the cerebrum sensation and volition and in the cerebellum the ability to maintain equilibrium, whilst Legallois believed that volitional movement was regulated in the cerebellum. Remove the cerebrum, the cerebellum and finally the medulla oblongata each in turn and the animal is left with only reflex function, the complement of the functions of the nervous system as described by Bell, Flourens and Legallois.

Hall quickly extended his important concept of the reflex arc from the purely local one as observed in the trunk of the newt to the whole of the body, making use of numerous little animals which he carefully placed when rendered headless under a bell-jar so that they would not be disturbed by the environment. At his home in Manchester Square he maintained a fairly representative menagerie. Here he decapitated what he called "a lively snake" and he describes observations on a pole-axed horse and on a turtle the execution of which may judiciously have been entrusted to a chef. He now believed that both Legallois and Bell were wrong in claiming the medulla to be the source of the respiratory motion: it was, he said, merely the channel, the centre in fact of the arc. It was the centre, too, of reflexes connected with eye movements. "All this is wonderful" he wrote in the book which in 1836 he dedicated to his idol, Professor P. Ch. A. Louis, "and I believe hitherto quite unknown to physiologists". He described the anal reflex as follows . . . "Nerves which arise from the verge of the anus take their course to the spinal marrow; whence some mysterious influence is returned to the sphincter muscle". He too was awaiting the aid of the microscopists. Meanwhile he continued his studies on epilepsy, attempting to explain the malady on two separate bases.

Marshall Hall, although addicted to neologisms and obsessed with the importance of his discovery, was endowed with a critical mind and seems always to have been well informed. Already in 1836 he was well acquainted with Cruveilhier's views on "apoplexie capillaire". He supported Lallemand and Andral in opposing the view of Foville and others that affections of the corpus striatum induced paralysis of the lower limbs, and those of the thalamus of the upper limbs. He sided with these authors too in refuting the contention of Bouillaud that lesions of the anterior part of the cerebrum were characterized by a loss of the power of articulation: the concept of a dominant hemisphere was yet to come. He was perhaps not unaware of psychological mechanisms, for on the subject of brain atrophy, having described the symptoms of dementia and paralysis he says "There is much for the physiologist and the pathologist to investigate in the singular return to a sort of infantile existence".

He enlarged further on the reflex arc in his first Croonian lecture in 1850 by which time the experimentalist could reckon on the help of anæsthesia. "This living pathology," he wrote, "I recommend for further cultivation in the place of that mere *caput mortuum* as presented in post-mortem or it might be designated post-morbum appearances".

Marshall Hall, when he visited Paris, probably met Brown-Séquard, part of whose M.D. thesis had been on the reflex movements in batrachia and he would be familiar with the latter's "Experimental Researches Applied to Physiology and Pathology" published in 1853 and with the work being carried out jointly with Charles Robin in the laboratory in the Rue Saint Jacques. The first symptoms of Marshall Hall's œsophageal stricture began as early as 1839, and although he was active to the end, he died before Brown-Séquard realized the invitation to lecture at the Royal College of Surgeons in May 1858.

Brown-Séquard reported his classical experiments in hemisection of the cord in 1850 and succeeded entirely, where Galen appears to have partially failed, for the latter had paid attention only to motor paralysis and so had overlooked the fact of the crossing of the sensory pathways. Brown-Séquard's writings suggest that he was by nature assertive although not to the point of being dogmatic. He owed his physiological upbringing to Martin-Magron and his traditional outlook on clinical medicine probably to Trousseau. Animal experimentation, he told them in Lincoln's Inn Fields, must always be checked by reference to the pathological findings in human cases, and the reverse was necessary too. He was an obvious choice of physician to The National Hospital not only because of his experimental work on paralysis but also on account of a sustained interest in epilepsy, which strangely enough appears to have been stimulated by his observation (1856) that some of the guinea-pigs with transected cords developed this condition. Short though his stay in London was there is little doubt that he influenced Hughlings Jackson.

That remarkable book "Mind and Brain" by Thomas Laycock (1860) appeared in the very year The National Hospital opened its doors and in it the growing world of alienists and neurologists, amongst whom we already discern Hughlings Jackson, were treated to lengthy and didactic discourses on mental dynamics, metaphysics and on the principles of scientific psychology. The notorious experiments on mesmerism at University College Hospital in the year 1837 seem first to have provided Laycock with ideas on the reflex function of the brain and he had already referred to hysteria in his "Treatise on the Nervous Diseases of Women" (1840). In those days he was still at York, a frank and outspoken critic of current attitudes, a thinker—if at most times a rather muddled one—and a not very lucid writer. When Dr. W. B. Carpenter subsequently claimed priority for the discovery of the Law of Unconscious Cerebral Action he met with a vigorous rebuff from this spirited philosopher, whose main contribution to medicine may be regarded as a continuation of the reflex theme so successfully developed by Hall on foundations laid by Bell.

If the predominant influence on British neurology at the beginning of the nineteenth century may be taken as having emanated from Leyden via Edinburgh and from France, we see that by the middle of the century the emphasis had certainly shifted to the German-speaking world, only to return once again to France with Claude Bernard and the dynamic Charcot who, in 1882, was installed in the first chair of neurology in Paris, an important landmark in world neurology.

During that active period of the 'forties and 'fifties we see the influence of Rokitansky, Virchow and von Kölliker in pathology, of Liebig in chemistry, of Romberg in clinical neurology and of Müller, Ludwig, von Helmholtz, DuBois-Reymond and Pflüger in physiology. There had been big changes during these years. The neurologist had abandoned Galenic concepts in favour of a rational physiology secure on the basis of experimentation and with the invention of the pendulum myograph by von Helmholtz (1850), that genius who had already propounded the Law of the Conservation of Energy, the way was open for the measurement of the nervous impulse and all the discoveries that have followed on. The secrets of life were being revealed daily by means of the microscope, the test tube and the galvanometer.

The clinicians kept pace and applied each discovery of the physiologist to the diagnosis of disease. Although Russell Reynolds' formidable chapter on the elements of diagnosis (1855)—it must surely have warned off many an intending specialist in neurology—suggests that simple inspection still played a greater part than physical examination, he was very much alive to the importance of "diminished reflection". Von Helmholtz invented the ophthalmoscope in 1851, Strick had already in the year 1856 drawn attention to the value of the reflex as a diagnostic aid

(Neuberger, 1930), Brown-Séquard was making use of Weber's technique of two-point discrimination in 1853 if not before, while Amberg drew attention to the phenomenon of miosis and lack of pupillary response to light in locomotor ataxia as early as 1855 (Neuberger, 1930).

But let us not underrate the importance of British contributions to neurology which during the sixty years under review were not inconsiderable for in those days research was dependent upon individual and spontaneous effort, there being no university, Privy Council or trust monies available for the purpose. When that small yet important medical committee met for the first time in Queen Square they must have looked back with pride on their national heritage, as we do to-night, and with that spirit of enterprise and independence born of voluntary effort, planned their future and ours with confidence.

BIBLIOGRAPHY

ABERCROMBIE, J. (1828) Pathological and Practical Researches on Diseases of the Brain and the Spinal Cord. Edinburgh.

BADHAM, J. (1835) *Lond. med. Gaz.*, **17,** 215.

BAILLIE, M. (1799) The Morbid Anatomy of Some of the Most Important Parts of the Human Body. London.

BELL, C. (1811) Idea of a New Anatomy of the Brain. London. (Reproduced in *Med. Class.*, 1936, **1,** 105 and in Gordon-Taylor and Walls, 1958.)

—— (1821) *Phil. Trans.*, **111,** 398.

BRAZIER, M. A. B. (1959) In: Handbook of Physiology (Amer. Physiol. Soc.). Washington; Sect. 1, **1,** 29.

BRIGHT, R. (1831) Reports of Medical Cases. London.

BROWN-SÉQUARD, Ch.-E. (1851) *C.R. Soc. Biol., Paris*, **2,** 33.

—— (1853) Experimental Researches Applied to Physiology and Pathology. New York.

BRYDONE, P. (1757) *Phil. Trans.*, **50** (i), 695.

BURR, C. H. (1929) *Med. Life*, **36,** 109.

CARSWELL, R. (1838) Illustrations of the Elementary Forms of Disease. London.

CHEYNE, J. (1812) Cases of Apoplexy and Lethargy with Observations of Comatose Disease. London.

CLARKE, J. A. L. (1851) *Phil. Trans.*, **142,** 607.

CONN, H. J. (1953) Biological Stains. Geneva, N.Y.

COOKE, J. (1820–1823) A Treatise on Nervous Diseases. London.

COURVILLE, C. B. (1948) *Bull. Los Angeles neurol. Soc.*, **13,** 143.

DAVY, J. (1828) *Trans. med.-chir. Soc. Edinb.*, **3,** 230.

FARR, W. (1837) *Brit. med. Almanack, London*, p. 145.

FORBES, J., TWEEDIE, A., and CONNOLLY, J. (1833) The Cyclopædia of Practical Medicine. London.

FULTON, J. F. (1929) *Proc. R. Soc. Med.*, **23,** 152.

GORDON-TAYLOR, G., and WALLS, E. W. (1958) Sir Charles Bell, His Life and Times. Edinburgh.

GREEN, J. H. S. (1958) *Med. Hist.*, **2,** 120.

GREEN, P. H. (1835–6) *Lancet*, ii, 263.

GULL, W. (1856) *Guy's Hosp. Rep.*, **2,** 146,

—— (1858) *Guy's Hosp. Rep.*, **4,** 167.

GUTHRIE, L. G. (1921) The History of Neurology. London.

HALL, C. (1861) Memoirs of Marshall Hall. London.

HALL, M. (1833) *Phil. Trans.*, **123,** 635.

—— (1836) Lectures on the Nervous System and its Diseases. London.

—— (1850) Synopsis of the Diastaltic Nervous System. London.

—— (1852) Synopsis of Apoplexy and Epilepsy and Proposals for a Hospital for Epileptics. London.

HARE, E. S. (1838) *Lond. med. Gaz.*, **23,** 16.

HOFF, H. E., and KELLAWAY, P. (1952) *J. Hist. Med.*, **7,** 211.

HOME, E. (1799) *Phil. Trans.*, **89,** 1.

HOOPER, R. (1826) The Morbid Anatomy of the Human Brain. London.

HUGHES, A. (1959) A History of Cytology. London and New York.

LAYCOCK, T. (1860) Mind and Brain. Edinburgh.

LEGALLOIS, C. J. J. (1812) Expériences sur le Principe de la Vie. Paris.

LUMSDEN, W. (1841) *Lond. med. Gaz.*, **26,** 858.

MARSHAL, A. (1815) The Morbid Anatomy of the Brain in Mania and Hydrophobia. London.

MONRO, A. (1783) Observations on the Structure and Function of the Nervous System. Edinburgh.

NEUBERGER, M. (1930) Essays in the History of Medicine. New York.

—— (1934) *Med. Life*, **41,** 542.

OLMSTEAD, J. M. D. (1944) François Magendie. New York.

—— (1946) Charles-Edouard Brown-Séquard (1817–1894). Baltimore.

PAGET, J. (1846) *Lond. med. Gaz.*, **37,** 522.

—— (1850) *Lond. med. Gaz.*, **45,** 229.

PARKINSON, J. (1817) An Essay on the Shaking Palsy. London.

PHILIP, A. P. W. (1815) *Phil. Trans.*, **105,** 424.

RADCLIFFE, C. B. (1854) Epilepsy and other Affections of the Nervous System which are marked by Tremor, Convulsions and Spasm. London.

—— (1858) Epilepsy and other Convulsive Affections. London.

REYNOLDS, J. R. (1855) The Diagnosis of Diseases of the Brain, Spinal Cord, Nerves and their Appendages. London.

RIESE, W. (1959) A History of Neurology. New York.

ROMBERG, M. H. (1853) Diseases of the Nervous System (Lehrbuch der Nerven Krankheiten des Menschen, 1840). Trans. and ed. by E. H. Sieveking. London.

SWAN, J. (1850) *Lond. med. Gaz.*, **45,** 845.

TODD, R. B. (1854) Clinical Lectures on Paralysis, Disease of the Brain and other Affections of the Nervous System. London.

WARD, O. (1846) *Lond. med. Gaz.*, **37,** 575.

WATSON, T. (1845) Lectures on the Principles and Practice of Medicine. 2nd Ed. London.

WHYTT, R. (1768) Observations on the Dropsy in the Brain. Edinburgh.

WISHART, J. H. (1822) *Edinb. med. surg. J.*, **18,** 393.

Hughlings Jackson, the Man; and the Early Days of the National Hospital

By MACDONALD CRITCHLEY, M.D.
London

THE paternal forebears of Hughlings Jackson were prosperous farmers and landowners in the North Riding of Yorkshire. The Jackson family can be traced directly back to 1707 when William Jackson was baptized at Brent Burnt of Harewood Bridge. The Jacksons were also maltsters in a small way, and there is a Charter dated 1749 licensing Thornton Jackson and Thomas Jackson to brew ale. Their more remote ancestry was of the same respectable yeoman stock. There was a George Jackson in the sixteenth century, one of whose daughters married Thomas Appleyard, the Mayor of York; another daughter married Luke Thurscroft, the Mayor of Hull; while his son married the granddaughter of Sir Richard Bowes. Jackson's mother, Sarah Hughlings, was a Welshwoman from Llanfintangel Rhyithon, in Radnorshire, near Newtown and Rhayadr. One of her ancestors was Benjamin Hewling, whose two sons were executed in 1685 for their participation in the Duke of Monmouth's rebellion[1]. Their elder sister Hannah had courageously but unavailingly interceded with Churchill and King James II. A year later, she married Henry, a grandson of Oliver Cromwell[2].

Jackson's three brothers and his sister emigrated to New Zealand early in adulthood, their father having lost a great deal of money from a slump in railway stock. The eldest brother, William, attained distinction in the Maori wars, where with the rank of major he commanded the first company of "Jackson's Forest Rangers". He married, but there was no issue. During the fighting a precious Maori flag was captured which Mrs. Jackson concealed by wearing it as a petticoat. This gallant undergarment is displayed at the present time in the Auckland Public Library. Thomas, another brother, became a junior officer in a ship sailing from San Francisco to New Zealand. Most of the other officers and the crew deserted to the goldfields of California, and the responsibility of bringing the ship into the home-port fell upon the young and inexperienced Thomas Jackson. The Company accorded him accelerated promotion and he commanded a troopship in the Crimean War. He gave up the sea, however, and settled in New Zealand as a sheep farmer; married and had a large family, the elder members of which migrated to the United States. Their offspring still live in and

[1]The two young men were apprehended after the Battle of Sedgmore, and became victims of Judge Jefferies' Bloody Assize. We learn from Noble (1787) "After the army dispersed, the two unfortunate brothers continued together and took the first opportunity of putting to sea, but they were driven back again, and with difficulty gained land, by climbing over the dangerous rocks. But the prospect now before them, was as melancholy as that from which they had just fled; the country was filled with soldiers, and those who had been raised to seize upon Monmouth's partizans; wherefore fearing to fall into the hands of the soldiery or the rabble, they surrendered themselves to a gentleman whose house was near the place they landed at; from whence they were sent to Exeter prison, July 12th; and on the 27th following, were put on board the Swan frigate, and conveyed to the Thames, from whence they were taken to Newgate; from which prison they were removed to Salisbury, then to Dorchester, where mr. Will. Hewling was tried and condemned and sent with several others to Lyme, where he was executed sept 12 1685. Mr. Benj. Hewling was tried and executed, with many others, at Taunton, where he was put to death, sept 30 some days after his brother. Of all the unhappy victims that died in the West none were more pitied than these two brothers; their youth, their beauty, their being the only sons of their mother, and she a widow, their extraordinary piety, resignation, even excessive joy at their approaching fate, made all men look up with horror at a throne, which, instead of being that of mercy, was not only that of severe justice, but excessive cruelty; for they were flattered with life; though not even one (which was earnestly desired) was saved. They were treated with the greatest inhumanity, and even shameful barbarity; for in Newgate they were loaded with heavy irons, not permitted to be together, nor to have any of their friends see them, even in the presence of the keeper of the prison; when the eldest was taken to execution, the Sheriff, callous to every feeling of humanity, would scarce permit him, and his fellow-unfortunates to take leave of their friends. At the fatal tree, . . . he would not permit mr. Hewling to pray apart, though it was particularly requested, but asked him if he would pray for the King, to which he answered 'I pray for all men;' and when the brutish Sheriff was asked permission for them to sing a psalm, he replied, 'It must be with ropes about their necks'; to this they cheerfully complied. The sorrowing spectators exclaimed, 'it both broke and rejoiced their hearts'."

[2]According to the martyrology, "Mr. Benjamin, the elder, reconciled the *lamb* and the *lion* exactly. In the field he seemed made only for war; and anywhere else, for nothing but love. He, without flattery, deserved to be called a very *fine man*, of lovely proportion, extremely well made, so handsome a mien, and good an air, as perhaps few in England exceeded him. His picture (a print is given in the martyrology) is pretty like him."

"The younger, mr. William, somewhat taller and more slender, his face fresh and lively as his spirit, being master of an extraordinary vivacity and briskness of temper. Both of them virtuous, pious, and courageous, far above their years, and indeed they seemed to be *men* too soon, one of them not being twenty, the eldest but two-and-twenty, when they died; verifying that common observation, that whatever is perfect sooner than ordinary, has generally a shorter period prefixed to it than what's more base and ignoble".

around the City of Oakland, California. The other members of the family prospered in New Zealand, and among the descendants are two doctors both of whom have, within the past twenty-five years, studied as post-graduates at the National Hospital, Queen Square.

Thus it happens that no direct descendants of Jackson's parents are to be found in this country. The sole representatives of the clan over here are the descendants of Hughlings Jackson's grandfather, Charles.

In 1835 the future Dr. John Hughlings Jackson was born at Providence Green, Green Hammerton, midway between York and Harrogate. He was the youngest of four boys and one girl. His education took place at the local village school, and later at Tadcaster. For a time he also went to school at Nailsworth in Gloucestershire, though why he should have gone so far afield is quite obscure. Hughlings Jackson is said to have been the least robust in his family, and far and away the most intelligent. However, his formal education was apparently quite inadequate, and Jackson in later years would comment adversely upon the schools he had attended, attributing his eventual success to the fact that he had not been over-educated.

At the age of 15, Jackson left school and became an apprentice to a general practitioner in the City of York, Dr. William Charles Anderson. He, with his son Dr. Tempest Anderson were well known throughout the North Riding for nearly a century. Their house at No. 23 Stonegate now forms the premises of the York Medical Society. Two years later, Jackson entered the York Medical School, which was later made redundant by the University of Leeds. In 1855 he spent some months in London attending courses at St. Bartholomew's Hospital, where he came under the spell of Sir James Paget. Unfortunately the hospital archives contain no record whatsoever of Jackson's student career. On April 10, 1856, Jackson presented himself at the Apothecaries' Hall in Black Friars Lane to sit the final examination for his licentiate, his examiner being Mr. Ansell. The City of London records preserved in the Guildhall show that the teachers who had signed him up for his examination had been Dr. Proctor in Chemistry and Forensic Medicine; Messrs. Allen, North and Hornby in Anatomy; Caleb Williams in Materia Medica; Mr. Moore in Botany; Dr. Allen and Dr. Anderson in Midwifery; Dr. Laycock in Medicine; and Dr. Sampson and Dr. Ley for clinical work. He also assisted at Dr. Paley's demonstrations of Morbid Anatomy. For eighteen months he had attended the York County Hospital in the capacity of a "probationary practitioner". Jackson was successful in obtaining his licence and a few months later he also achieved the diploma of membership of the Royal College of Surgeons of England.

When qualified, Jackson returned to York where for the next two and a half years he held the post of resident medical officer at the City Dispensary (Fig. 1). The clinical experience was valuable, and we have evidence that the neurological cases which came to his notice at that time made a significant impression upon his imagination. Here he also acquired scientific methods of verifying his clinical judgment, and he regularly attended pathological sessions where he and his chiefs went over the cases which had come to autopsy the week before, re-assessing the clinical evidence in the light of the morbid findings.

At this time Jackson came under the influence of a teacher of quite exceptional order. This was Thomas Laycock (Fig. 2) who was destined to leave York for the Chair of Clinical Medicine at Edinburgh. It was during this later period in Scotland that Laycock was to meet young David Ferrier whom he also orientated towards neurology. Laycock was an old-fashioned but thoughtful physician who had been much impressed by Marshall Hall, whose conception of reflex action was being looked upon as unorthodox and unsound. Doubtless these ideas were transmitted by Laycock to the young houseman, Hughlings Jackson.

In September 1860 Jackson proceeded to St. Andrews to sit for the M.D. examination along with 44 others. He was among the 36 who were successful. This was almost the last occasion when the M.D. was awarded to external students under the 1826 amendment of the regulations which dated from the original Papal Bull of Foundation in 1413. In 1862 the regulations for the Doctorate at St. Andrews were changed once again.

Jackson had moved to London in 1859 where he stayed with his older friend and fellow-graduate, Jonathan Hutchinson, at No. 4 Finsbury Circus (Fig. 3). At this time Jackson was becoming more and more immersed in pure philosophy and he was attracted profoundly by the teachings of Herbert Spencer (Fig. 4), and particularly by his views on evolution. He had at one time thought of abandoning medicine altogether in favour of academic philosophy. Hutchinson dissuaded him and helped direct his special aptitudes into a study of the normal and pathological functions of the nervous system, a topic which at that time was obscure. It was Hutchinson too who helped Jackson earn a living by joining him in medical journalism. They both worked for a time as reporters on the *Medical Times and Gazette*. Their duties took

FIG. 1.—The York Dispensary when Hughlings Jackson was a Resident Medical Officer. (Reproduced from O. Allen's "History of the York Dispensary". York, 1845.)

FIG. 3.—Finsbury Circus. Hughlings Jackson and Jonathan Hutchinson lived at No. 4.

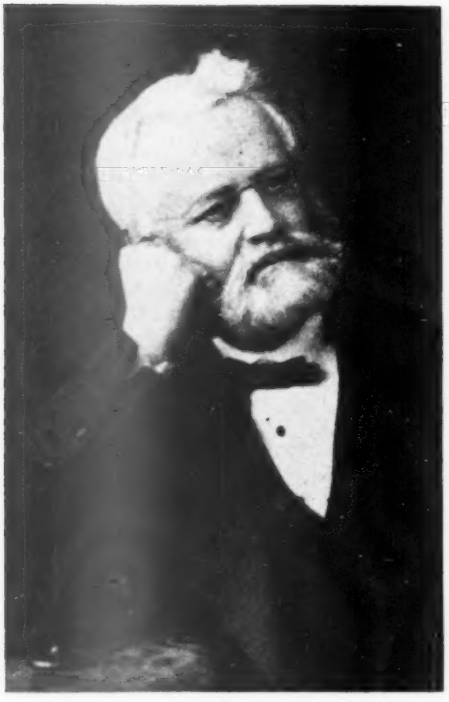
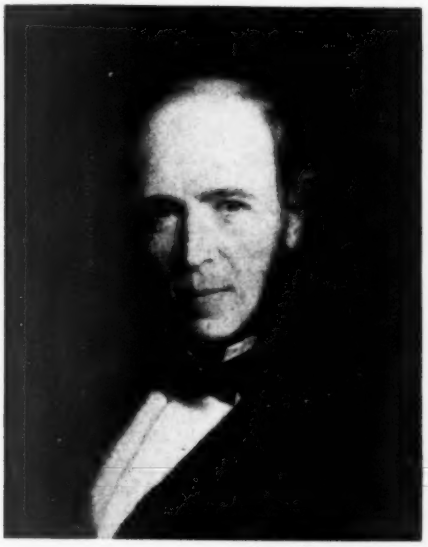


FIG. 2.—Dr. Thomas Laycock.



National Portrait Gallery

FIG. 4.—Herbert Spencer.

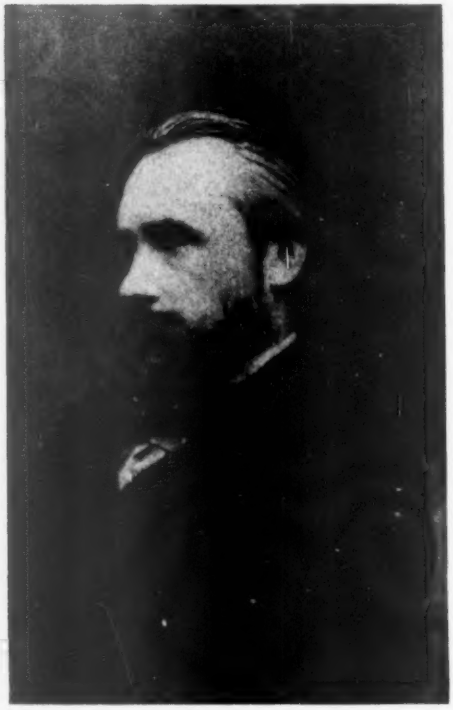


FIG. 5.—Hughlings Jackson as a young man.

them to various medical meetings throughout London, where they had the good fortune not only of seeing picked clinical problems, but also of meeting the most distinguished medical men in town.

The friendship of Jackson and Hutchinson was life long. They would go for week-end country rambles. Hutchinson was best-man at Jackson's wedding. It was said that Jackson weaned Hutchinson of some of the last traits of narrow sectarian thought that still lingered, promoting a more philosophical outlook and giving greater clearness to his thought.

Jackson's interests were becoming more and more attracted towards nervous disease. His future career was eventually determined by a meeting with Brown-Séquard, who in 1860 had joined J. Z. Ramskill to become the original physicians to the newly founded National Hospital for the Paralysed and Epileptic in Queen Square. The rapid growth of this hospital soon necessitated an increase in the staff. In July 1861 the need for an Assistant Physician was brought to the notice of the Board of Management, only to be shelved. The matter was again formally raised in April 1862 by Dr. Ramskill who suggested, on behalf of himself and his co-Physician, that the time had come when increased medical assistance was required. The lay members stalled, however, and turned to the next item on their agenda, which concerned estimates for the erection of a water-closet in the passage leading to the female ward. On May 7, 1862, the matter was ventilated again and this time settled, when Brown-Séquard proposed, and Mr. Norman Wilkinson seconded, that Dr. Hughlings Jackson "be and is hereby elected Assistant Physician to the National Hospital, on the understanding that he should visit the hospital twice a day, and also see all the out-patients at their own homes; for which extra services he was to be allowed the remuneration of £50 per annum".

Two months later Jackson asked to be relieved of his domiciliary duties and to sacrifice his salary. It seems that little attention was paid to this request which we find reiterated twelve months later. When Brown-Séquard resigned his appointment in July 1863 the need for additional medical staff was again a matter for discussion. Not until a year later were two further full physicians appointed. There were four applicants, Russell Reynolds and Henry Sieveking, who were each elected, while Jackson and Ogle were unsuccessful. In September 1864 Dr. Victor Bazire was elected second assistant physician. The allocation of duties of the staff put Jackson in charge of the Friday clinics: the suggestion was made that he should be called a "Junior Physician" but this motion was not carried. Not until 1867 did Jackson eventually attain the status of full Physician.

Perhaps it was because of his youth that Jackson's earliest days at the National Hospital seem to have been unpropitious. When he joined as Assistant Physician, his colleagues were Ramskill and Brown-Séquard. When Jackson was eventually promoted at the age of 32 the staff comprised Ramskill, Radcliffe, Russell Reynolds, Sieveking and Bazire, Jackson was obviously an intellectual giant among these. But it is not with Jackson's place in neurology that we are concerned here, for that subject is familiar enough.

In 1863 Jackson also became Assistant Physician to the Metropolitan City Hospital, but gave this up two years later when he joined the staff of the London Hospital where his friend Hutchinson and his colleague Ramskill were already installed. It was at this juncture that Jackson left Finsbury Circus to reside at No. 5 Queen Square, then at No. 28 Bedford Place (Fig. 6), and finally at No. 3 Manchester Square.

In 1865 he married his cousin Elizabeth Dade Jackson, an authoress of slight children's tales.

The marriage was without issue. Though supremely happy it was short and tragic. Mrs. Jackson fell a victim to a cerebral thrombophlebitis, causing frequent focal seizures. When she died in 1876, Jackson's loneliness was great and inconsolable. Ten years later we find Jonathan Hutchinson writing to his son: "Dr. Jackson and I had a pleasant walk in the Park and Zoo yesterday morning; we did not look at anything in the latter, but simply talked. He seemed to have pleasure in going back to old times, and talked much about his wife, whom he still very bitterly regrets. All would be well with him if she were only living."

Jackson was always too shy and self-effacing a man to be sociable or clubbable. He had only a few cronies, like Hutchinson and Thomas Buzzard. Later in life he saw a great deal of his young colleague James Taylor, who had what must have been a remarkable experience in devilling for both Gowers and Jackson in succession. Jackson's supreme modesty—almost humility—made him courteous and tolerant to a fault. In his writings he leaned over backwards to recognize even the most trivial help from his colleagues and house physicians. Some of these acknowledgments strike us to-day as almost studied and unnecessary: but they were always sincere. His toleration is also shown in the generous manner in which he strained to mention co-workers who were actually far removed from him in thought and achievement. This is shown by his references to Broca and to Bastian, though one turns in vain the pages of these authors for any reciprocation on their part.

FIG. 7.—Hughlings Jackson from a bust at the National Hospital, Queen Square.

FIG. 6.—28, Bedford Place, W.C.1, where Jackson lived for a time.

If Jackson was too diffident to make many acquaintances, he had no enemies. Indeed he was a gentle and much beloved physician, especially in his old age when he had become a living legend; idolized, respected, but perhaps not fully comprehended. This was at a time when he had become the "Sage of Manchester Square" as well as the acclaimed Master, the father of British neurology. We search in vain for any Cromwellian qualities of harshness which he ran the risk of inheriting. The only subject upon which he would become heated concerned his education, saying that his schoolmasters had not been fit to sell penny pies on street corners. He lived to find his colleagues, hard individualists though they were, subscribe to a portrait by Lance Calkin which hangs in

the London Hospital; and to a bust which stands in the vestibule of the National Hospital (Fig. 7). There was also established in his own time a Hughlings Jackson medal and lectureship, of which he was the first recipient.

An odd paradox lies in the discrepancy between the profundity of his philosophic thinking, and the lack of what we might call culture. His formal schooling had ceased very early. Apparently his knowledge of languages was slight. He had no classical foundation. Literature, music and the arts meant nothing at all to him. True, he possessed a library, but it would have shocked any bibliophile. There were technical works, but annotated, mutilated, mauled and graingerized. Jackson was known to borrow from his colleagues, tear out the relevant pages, and omit to return the book. Most of his reading consisted in the two-shilling yellow-backs; the shockers, thrillers, Westerns of the Victorian era. His reading technique is well known. He was liable to tear the book into two and stuff each half into the left and right coat-pockets. As each leaf was read it was discarded. In this manner he whiled away a train journey, or even the carriage-ride to the Whitechapel Road.

Some of the eccentricities were bound up with his desire to avoid situations fraught with possible boredom. He was too restless to attend lectures, or even places of entertainment.

An unfortunate failing of Jackson's was his obscurity. His colossal ideas were only belatedly recognized, for want of an interpreter. Not only a poor public speaker, he was no writer either. Like Ibsen, he would start a paper with a vague idea, and then go over the manuscript again and again; adding, qualifying, emending, but never condensing. The complexity of his writing shows an obsessional trait but not necessarily a quest for exactitude. This is illustrated by his persistent misspelling of the name of Dr. Auburtin, the inspirer of Broca. The use of footnotes amounted to an abuse. One can scarcely credit the untidiness of his MSS, which must have been the despair of the typesetters. But if he was no lord of language, he was masterly at creating an apt and felicitous turn of expression. These may be taken as suggestive that Jackson might have been something of a wit. This is open to argument. He certainly possessed a sense of humour. Unquestionably he was intellectually interested in the problem of jesting and joking, no doubt inspired by Herbert Spencer. But if he is to be reckoned as a wit, it is only in the heavy and mannered style which we associate with the Senior Common Rooms of the older Universities. He never scintillated, like Sydney Smith, Gilbert, Whistler or Wilde.

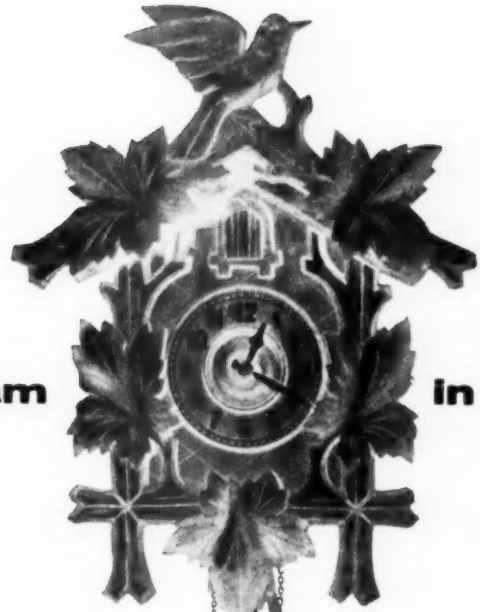
In later life, loneliness and increasing deafness made him something of a recluse. Like John Hunter he was liable to attacks of vertigo. He became somewhat vague and absent-minded. As Senior Physician to the London Hospital the duty had devolved on him to conduct Queen Victoria around the wards; he did not appear, however, for the arrival of a relative from New Zealand put the function out of his head. A remote cousin, Charles, used to keep a watchful eye on him at his home, with James Taylor and Gordon Holmes in the offing. He would allow no female housekeeper around him and the rare visitors to a meal recall that his late wife's place, flanked by chairs on either side, would be kept vacant, Jackson and his guests sitting opposite. He would often take carriage drives around London, sometimes accompanied by the little daughters of cousin Charles: sometimes by one of the Residents at Queen Square. In the latter event Jackson had the disturbing tendency to drop off the house officer in a remote suburb, leaving him to make his way home as best he could.

Jackson's end when it came early in October 1911 was a peaceful one. He left an unforgettable stamp upon our neurological discipline. His life-long friend, Jonathan Hutchinson described Jackson as "the nearest to a genius that it is my privilege to have known". His memory as a wise and kindly philosopher is still green. Bacon's appraisal would appear appropriate for Hughlings Jackson:

> ". . . The men of experiment are like the ant; they only collect and use: the reasoners resemble the spiders, who make cobwebs out of their own substance. But the bee takes the middle course, it gathers its material from the flowers of the garden and of the field but transforms and digests it by a power of its own. Not unlike this is the true business of philosophy . . ."

REFERENCE

NOBLE, M. (1787) Memoirs of the Protectorial House of Cromwell, London.



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Section of Pathology

President—Professor R. J. V. PULVERTAFT O.B.E., M.D.

Meeting
January 19, 1960

MEETING HELD AT THE LONDON HOSPITAL (BERNHARD BARON INSTITUTE), LONDON

THE following demonstrations were given:

Cell Cultures of Inclusion Conjunctivitis Virus.—C. F. BARWELL and J. WHITTINGTON.

Unexpected Death in Infancy: A Planned Research Project Based upon Coroner's Autopsies.—F. E. CAMPS.

(1) **Rheumatic Heart Disease in Nigerians.** (2) **Skeletal Changes in Rats in Amino-nitrile Poisoning.**—J. W. LANDELLS.

Acute Fatty Liver in Pregnancy.—R. G. F. PARKER.

(1) **Unmasking of Latent Effects of Irradiation in Rat's Liver.** (2) **Chemical Mechanisms in Liver Regeneration.** (3) **Stability of Pituitary Thyrotrophic Cells in Long-term Castration.**—K. WEINBREN.

Two Cases for Discussion: (1) Combined Fungus Infection and Sarcoidosis. (2) **Collagen Disease with Renal Amyloidosis.**—A. H. E. MARSHALL.

Mediastinal Enteric Cysts Associated with Vertebral Anomalies.—P. G. I. STOVIN.

Histochemical Study of Turban Tumours.—P. G. I. STOVIN and K. SWETTENHAM.

Oxalosis.—D. T. D. HUGHES (*see J. clin. Path.*, 1959, **12,** 498).

A Modification for the Differential Staining of Pituitary Basophil Cells in Rat and Man.—K. SWETTENHAM (*see J. clin. Path.*, 1960, **13,** 888).

Reducing Properties of Bile Pigment.—H. J. OLIVER, K. SWETTENHAM and M. WRIGHT.

Prolongation of Survival of Differentiated Cells in Pituitary Autografts.—J. WISLAWSKI and K. WEINBREN.

Meeting
February 2, 1960

A JOINT MEETING was held with the Section of Medicine when there was a discussion on **The Pathologist and the Patient.** The discussion was opened by Professor ALAN KEKWICK, Professor J. W. S. BLACKLOCK and Dr. R. R. WILSON.

Dr. E. R. CULLINAN (President of the Section of Medicine) was in the Chair.

Meeting
February 16, 1960

MEETING AT THE ROYAL ARMY MEDICAL COLLEGE, MILLBANK, LONDON

THE following demonstrations were given:

Histology: (1) Granulomatous Reactions in Lymphatic Glands. (2) **Disseminated Non-necrotizing Vasculitis.**—Lieutenant-Colonel D. W. BELL (Leishman Laboratory).

A Simple Hand-operated Bellows Resuscitator.—Lieutenant-Colonel H. W. WHITCHER (War Office).

Acute Lethality in Irradiated Mice.—Lieutenant-Colonel J. A. H. BROWN, in collaboration with Mr. R. WESTGARTH (Harwell).

Bacteriology of the Irradiated Mouse.—Lieutenant-Colonel J. A. H. BROWN (Harwell).

The Wet-film Technique in Neurosurgery.—Captain D. C. ROBSON (Military Hospital, Wheatley).

Estimation of Serum Calcium by Automatic Titration.—Major I. D. P. WOOTTON (Postgraduate Medical School).

Some Lesser-known Parasites.—Brigadier L. R. S. MACFARLANE (Royal Army Medical College).

(1) **Production of Diagnostic Sera and Suspensions.** (2) **Identification of Enterobacteriaceæ.** (3) **Sterility Tests for Intravenous Crystalloids.**—Major M. M. MUNRO (David Bruce Laboratories).

(1) **Preparation of Vaccines (with Special Reference to T.A.B.T. Intradermal).** (2) **Artificial Mouse (used in Experiments of Disinfection of Syringes).**—Major E. E. VELLA (David Bruce Laboratories).

Transfusion Panniers Nos. 1 and 2.—Colonel M. H. P. SAYERS (David Bruce Laboratories).

(1) **Thyroid Cell Tissue Culture.** (2) **Respiratory Virus Infections in the Army.**—Major R. J. C. HART (Royal Army Medical College).

Modern Views on the Hæmoglobin Molecule.—Major H. LEHMANN (St. Bartholomew's Hospital).

Meeting
March 1, 1960

THE following papers were read:

Human Genetics and Disease.—Professor L. S. PENROSE.

Familial Deficiency of Pseudocholinesterase.—Dr. H. LEHMANN.

Galactosæmia—a Hereditary Disease.—Dr. A. HOLZEL.

Meeting
March 15, 1960

DNA and Biological Research

By W. HAYES, M.B., Sc.D., F.R.C.P.I.
London

ALTHOUGH it had been known for some time that nucleoprotein was the predominant constituent of chromosomes, the clear demonstration that the transmission of hereditary characters was probably a function of the nucleic acid itself awaited three kinds of definitive experiment in bacterial and virus genetics. The first (Avery *et al.*, 1944) was the discovery that virtually pure, highly polymerized DNA extracted from the cells of one strain of pneumococcus is able to induce permanent hereditary changes in the cells of a second strain to which it is added, with respect to those characters in which the two strains differ. The ability of DNA to transmit genetic characters in this way is completely and specifically destroyed by the enzyme deoxyribonuclease. Moreover, the higher the degree of purification of the DNA, the greater becomes its efficiency in transformation.

The second type of experiment was the classical one carried out by Hershey and Chase (1952) with a virulent bacterial virus or bacteriophage. The anatomy of bacterial viruses, as revealed by electron microscopy, is quite complicated. In essence, these viruses are made up of a protein sheath in the form of a hexagonal head enclosing a very long filament of DNA, and a tail which terminates in a plate from which extend six fibrils whereby the virus attaches itself to the bacterial cell wall. When the protein coat of the virus is specifically labelled with radioactive sulphur, S^{35}, or with C^{14}, and its DNA with radioactive phosphorus, P^{32}, it can be shown that, on infection of sensitive bacteria, only the virus DNA and about 1% of its protein enters the bacterial cell. The protein sheath remains outside the cell and, once the DNA has been injected, can be stripped off with a blendor without altering the course of the infection. After injection, the phage DNA behaves like a "master gene" which redirects the chemical machinery of the cell to the exclusive manufacture not only of new virus DNA, but also of new virus protein so that within twenty minutes the cell bursts and liberates several hundred mature virus particles. Unlike the injected DNA, none of the 1% of initially injected virus protein appears in the progeny particles.

The third type of experiment concerns not DNA but RNA. Many animal and plant viruses are composed of protein and RNA and are devoid of DNA. Tobacco mosaic virus, for example, consists of a protein rod with an axial hole running through it, the RNA being arranged in a single helix running throughout the length of the rod periaxially. The work of Gierer and Schramm (1956) and Fraenkel-Conrat *et al.* (1957), using quite different methods, revealed that when tobacco mosaic virus is fractionated chemically, separating the protein from the RNA, the RNA is infective by itself while the protein is not. The infectivity of the RNA is rapidly and specifically destroyed by ribonuclease but is not affected by antiserum against the virus protein. These findings have recently been confirmed for a number of other small RNA viruses which are animal pathogens. A significant corollary to this work was the finding by Fraenkel-Conrat and Williams (1955) that, when separated and purified virus RNA and protein are mixed together in a test-tube, fully infective virus particles reform automatically. Various strains of tobacco mosaic virus exist whose protein components differ both in antigenic structure and in amino-acid content. If two such strains of virus are chemically fractionated and the protein of one strain mixed with the RNA of the other, virus rods are reconstituted as before. When the plant is infected with these synthetic, hybrid viruses, the liberated progeny viruses are found to have protein of the same type as the nucleic acid, but different from the protein of the infecting particles.

These experiments provide, *in extenso*, very

good (though not conclusive) evidence for the working hypothesis that both DNA and RNA can carry all the specifications (or information) required for their own as well as for specific protein synthesis and are, in fact, the only repositories of this information in the cell. In other words, the genes of bacteria and their viruses (and probably, by inference, of all cells) are composed of DNA, while RNA serves the same function in the RNA viruses.

The next logical step, in the light of this evidence, is to consider DNA at the structural level in an attempt to find at least plausible answers to three vital questions: (1) How does DNA replicate? (2) How does it carry the specifications which define all the activities of the cell and ensure genetic continuity? (3) How is this information translated, or decoded, into functional biochemical terms?

Nowadays it is almost impossible to discuss basic genetic mechanisms in a constructive way without thinking in terms of the now generally accepted model for DNA structure proposed by Watson and Crick (1953).

Chemical analysis had shown that DNA is a very long-chain polymer built up of alternating deoxyribose-sugar and phosphate molecules. To each sugar is attached a nitrogenous base of which there are four kinds: the two purines, adenine (A) and guanine (G), and the two pyrimidines, thymine (T) and cytosine (C). Each unit of the polymer, consisting of base-sugar-phosphate, is called a *nucleotide* so that the polymer is a polynucleotide (Fig. 1*a*). A striking feature of the chemical composition of DNA is that the ratio of purine to pyrimidine bases is unity, i.e., that A+G=T+C.

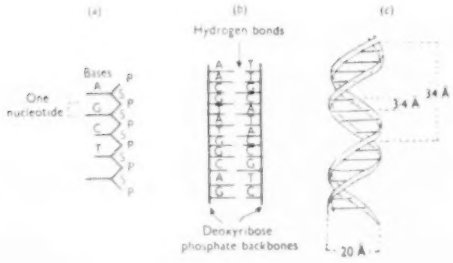

FIG. 1.—Diagrammatic representation of the physico-chemical structure of DNA (*see* text). P=phosphate. S=deoxyribose sugar. A, G=adenine, guanine (purine bases). T, C=thymine, cytosine (pyrimidine bases).

The next step forward resulted from the use of X-ray diffraction analysis which suggested that the polymer has three essential structural features: (1) The bases, which are flat structures, are arranged at right angles to the long axis of the DNA fibre and are stacked one above the other like "a pile of pennies". (2) The fibre is arranged helically. (3) The fibre consists of more than one polynucleotide chain.

The Watson-Crick model was designed to accommodate all these facts. It comprises two polynucleotide chains, of which the alternating sugar-phosphate molecules form the backbones, while the flat bases on each chain face inwards towards one another and are coupled together by hydrogen bonds (Fig. 1*b*). The two chains are then twisted around one another to form a double helix, being interwoven in such a way that they can only be separated by unwinding (Fig. 1*c*). In fact, the structure can be represented as a ladder, the uprights being the sugar-phosphate backbones and the rungs the paired bases, the two ends of the ladder then being twisted in opposite directions; each rung is, of course, sawn through and then stuck together with glue which represents the hydrogen bonds weakly joining the paired bases. The diameter of the double helix is 20 Å, the distance between each pair of bases 3·4 Å, while one complete turn extends about 34 Å along the long axis, i.e. there are ten pairs of bases per turn.

The most important feature of this model is that the bases must be *specifically* paired; if two purines are paired together their dimensions are too great to fit the constant diameter of the double helix, while the dimensions of paired pyrimidines are too small. Assuming the most stable distribution of hydrogen atoms on the bases, then adenine can pair only with thymine, and guanine with cytosine, although no restriction whatsoever is imposed on the sequence of A, G, T and C along any one chain (*see* Fig. 1*b*). This specific pairing of purine and pyrimidine bases is not only structurally necessary, but also meets the requirement of chemical analysis that the ratio of purine to pyrimidine bases should be unity.

Now let us examine this model from the point of view of the functional requirements of genetic material.

Replication.—From the specificity of base pairing it is obvious that the sequence of bases on either chain determines that on the other, so that each chain of the double helix can serve as a template for the synthesis of the opposite chain and, therefore, of a complete new double helix. All

that is required is that the strands should unwind and separate so that freshly synthesized nucleotides can bond themselves specifically to the appropriate base on each original chain. Polymerization of the nucleotide backbones would then lead to two pairs of chains, each identical with the original. This mode of replication is called *semi-conservative* since each daughter duplex consists of one chain conserved from the parent duplex and one newly synthesized chain. This is a beautiful scheme, but is it true? To find how replication actually occurs, the most obvious approach is to label the DNA of living cells, such as bacteria, and then observe how the labelled atoms are distributed among the DNA molecules of the progeny after replication. The first experiment of this kind to give a clear-cut result was done by Meselson and Stahl (1958).

If a solution of cæsium chloride is centrifuged at high speed for a long time in a Spinco ultracentrifuge, an equilibrium is reached in which the centrifugal force tending to deposit the cæsium molecules is counter-balanced by diffusion which tends to disperse them. This leads to a density gradient in the solution. It so happens that the density of DNA molecules lies within this gradient so that if DNA is mixed with the cæsium and centrifuged it will float at its own buoyant density level, like a balloon in air, and will thus be concentrated into a discrete band. The method is so sensitive that if normal DNA is mixed with DNA in which the nitrogen of the bases has been replaced by heavy nitrogen, N^{15}, and the mixture is centrifuged, the two DNAs will separate into two well-defined bands, in the same way that balloons filled with either hydrogen or helium will rise to different levels in the atmosphere.

The experiment was as follows: *Escherichia coli* was grown for many generations in a medium containing N^{15} as the only source of nitrogen so that all the N^{14} of the cells, including that in the DNA bases, was replaced by the heavy N^{15}. The cells were then washed, transferred to a medium containing only N^{14} and allowed to multiply. At intervals during several generations thereafter, samples of cells were removed and their DNA extracted and analysed for N^{14} and N^{15} content in a cæsium chloride gradient. The kind of result we would expect to find if the DNA molecules replicated semi-conservatively is shown in Fig. 2.

At the beginning of the experiment, both strands of each DNA duplex contain only N^{15}. The strands then unwind and each serves as a template for the synthesis of a new, complementary strand. Since this first replication takes place in N^{14} medium, however, these new strands should incorporate only N^{14} so that each daughter duplex should be hybrid, one strand containing N^{15} and the other N^{14} DNA. At the end of the next generation, and subsequent ones, the number of hybrid molecules should remain constant, while pure N^{14} molecules should begin to appear. This is just the result that the actual experiment revealed, so that the theoretical predictions are completely fulfilled. Hybrid DNA molecules have also been obtained from the replication of various types of bacterial virus in their host cells.

Provided that the DNA molecules extracted in these experiments are really in the form of double helices and not, for example, aggregate pairs of duplexes, the results are entirely compatible with semi-conservative replication and incompatible with other proposed replication systems. There is now good evidence that the molecules are really double helices. For example, when the hybrid DNA is heated it breaks down into pure N^{14} and N^{15} molecules. These molecules behave like known single-stranded DNA when used as a primer in the Kornberg system, in which more or less specific DNA is synthesized *in vitro* from trinucleotide precursors provided priming DNA and purified polymerase extracted from *E. coli* cells are present.

Transport of genetic information.—Information necessary to specify all the functions of the cell must be carried by the genetic material in the form of a chemical code. The only possible irregularity in the Watson-Crick model of DNA which could serve as a code is the sequence of the four bases, adenine, guanine, thymine and cytosine, along one of the polynucleotide chains of the duplex. The first question is: How much is required of a genetic code? The answer can be

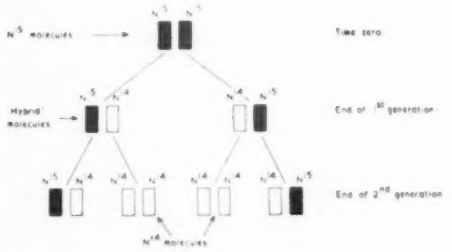

FIG. 2.—The distribution of heavy nitrogen (N^{15}) in DNA molecules, extracted from *E. coli* cells at intervals during multiplication in excess of N^{14}, as revealed by the density gradient method of Meselson and Stahl (1958). Each of the paired rectangles represents one of the polynucleotide chains of the DNA duplex.

put very simply as follows. The metabolism of living cells is mediated by a very large number of enzymes which are protein in nature. The specific activity of these proteins is a function of the *sequence* of twenty amino acids within the polypeptide chains of which they are composed. An alteration of this sequence, or even the substitution of a single amino acid by another—as Ingram (1957) has shown to result, in the case of hæmoglobin, from a single mutation affecting the code—may alter the specificity of the protein. The coding problem therefore resolves itself into how a linear sequence of four nucleotides can code for a linear array of 20 amino acids. This is called the *sequence hypothesis*. Theoretically, this hypothesis presents no difficulty, for from an alphabet of four letters can be made as many as 64 distinct words of three letters each. In fact Crick *et al.* (1957), by assuming certain necessary restrictions, such as that the code shall be non-overlapping, have shown that non-overlapping sequences of three nucleotides can determine *precisely twenty* unique amino-acid sequences. This is about as far as theory can take us. The actual solution of the code must be experimental; a correlation has to be established between the sequence of amino acids in a specific protein and the sequence of bases along the segment of DNA which determines its synthesis. Base sequence analysis has not yet progressed to the stage where a direct attack is possible. Nevertheless, several indirect lines of approach are now possible and are being explored. For example, fine structure genetic analysis in certain micro-organisms now permits the distinction and mapping of many different mutational sites which alter the code within a region of chromosome determining the synthesis of a single low molecular weight protein. A correlation between the order of such mutational changes along the chromosome and the sequence of amino acid substitutions in the derivative protein would afford proof of the sequence hypothesis.

In connexion with coding, does a small chromosome, such as that of *E. coli* which is at the limits of resolution of a light microscope, contain enough DNA to carry all the information required by the cell? A simple calculation will give an affirmative answer. It is almost certain that this chromosome exists as a single double helix of DNA. Two quite different methods of estimation show that it contains rather more than ten million double nucleotides. This means that, if extended, it would be about 1,000 times longer than the cell itself. If we assume that the average enzyme contains about 300 amino acids, which is an over-estimate, and that three nucleotides code for each amino acid, it works out that about 1,000 nucleotides are needed to code for each enzyme. It follows that the chromosome of *E. coli*, ten million nucleotides long, could carry specifications for the synthesis of some 10,000 different enzymes, provided all the DNA is genetically functional.

Mutation.—Watson and Crick (1953) put forward the idea that natural mutation could be explained on their model by assuming occasional unstable tautomeric shifts in the position of hydrogen atoms on the purine and pyrimidine bases. For example, Fig. 3*b* shows the most stable position of the hydrogen atoms on adenine which determines its specific pairing with thymine: Fig. 3*c* shows why hydrogen bonding between adenine and cytosine cannot occur. If, however, during replication the hydrogen atom should

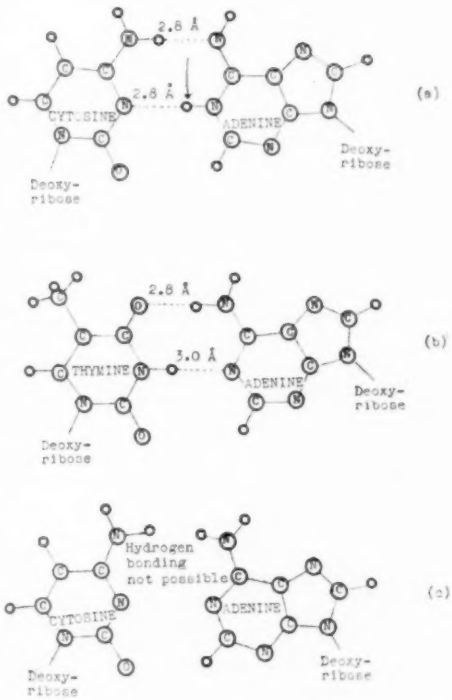

FIG. 3.—Determination of specific base pairing in DNA by hydrogen bonding. (*a*) Shows how a shift in the position of the hydrogen atom from the 6-amino to the N1 position on adenine can allow pairing with cytosine. (*b*) Shows the most stable position of the relevant hydrogen atom on adenine which determines its pairing with thymine. (*c*) Shows why adenine cannot normally hydrogen bond to cytosine without affecting the regularity of the double helix.

temporarily shift from the 6-amino to the nitrogen 1 position (Fig. 3*a*), then the adenine *will* specifically bond to cytosine instead of to thymine. At the next replication this cytosine will pair in the normal way with guanine so that, in all the descendants of this duplex, the original adenine-thymine base pair will be replaced by a guanine-cytosine pair and the code will be permanently altered at this point. One can well imagine the mutagenic effect of radiation energy on such a system.

Important new information about mutation has recently come from the finding that certain base analogues can act as efficient mutagens (*see* Brenner *et al.*, 1958). Thus, 5-bromouracil, an analogue of thymine, can pair with adenine and replace the thymine in DNA. The mutagenic action of such analogues not only correlates mutation with DNA structure but also offers a direct and specific approach to the coding problem. Genetic analysis of the sites of mutation involving a single function in bacteriophage T_4, which has a resolving power high enough to distinguish between adjacent nucleotide pairs, has shown that the sites at which spontaneous and acridine-induced mutations arise are different, in at least 90% of cases, from the sites of base analogue-induced mutations. This may mean that the code can be changed in two different, non-overlapping ways; for example, one way could be substitution of a purine by a purine (i.e. A—T to G—C), and the other, substitution of a purine by a pyrimidine (i.e. A—T to T—A or C—G) (Freese, 1959).

The most recent and most interesting chemical mutagen to be discovered is nitrous acid, which falls into the base analogue group. Nitrous acid acts by deaminating DNA and RNA bases in a specific way. Thus, on deamination, adenine is converted to hypoxanthine, guanine to xanthine and cytosine to uracil. There is evidence from tobacco mosaic virus that the majority of mutations may be due to substitutions of cytosine by uracil which is a normal RNA base. Nitrous acid is of special interest as the first mutagen to act *in vitro*, both on isolated tobacco mosaic virus RNA (Gierer and Mundry, 1958) and also on transforming DNA isolated from bacteria (Litman and Ephrussi-Taylor, 1959). This is because it acts directly in causing base substitution and so does not require replication for its effect.

I will conclude with a dogmatic summary of our views of how genetic information is translated into functional terms, so that specific protein is synthesized by the cell (review by Brown, 1960).

It is known that protein synthesis depends on the presence of RNA in the cell. DNA is essential for RNA synthesis which appears to be initiated in the nucleus, but protein can be made in the absence of DNA, provided RNA is present. There is good evidence that the site of protein synthesis is the small microsomal particles in the cytoplasm which consist of high molecular weight RNA in association with protein. RNA is chemically and structurally similar to DNA except that ribose replaces deoxyribose in its backbone, the base uracil replaces thymine, while it is probable that, in its functional state, it consists of a single instead of a double chain. We know from the RNA viruses that a single RNA chain can code for specific protein synthesis. From all this it is reasonable to guess that the microsomal RNA offers a template for protein synthesis and carries the code determining amino-acid sequence which was passed on to it by the DNA during its synthesis in the nucleus. The question then arises as to how the amino acids are lined up on this template.

Some very interesting recent work has shown that cells, ranging from liver cells to bacteria, have a second type of RNA called soluble RNA which differs from microsomal RNA in the following respects: (1) It is of low molecular weight and is composed of short chains about 100 nucleotides long. (2) Unlike the microsomal RNA it shows a high turnover. (3) Different types of soluble RNA exist for each amino acid. The amino acid, when activated by a specific enzyme, attaches itself specifically to a terminal adenine group of its homologous RNA molecule. (4) The molecules of soluble RNA with their attached amino acids are then rapidly transported to the microsomes where the amino acid becomes incorporated into protein.

It is plausible to suggest that each soluble RNA molecule may carry two codes. At one end would be the code enabling the molecule to recognize and bind its specific, activated amino acid; at the other end would be a mirror image of the microsomal sequence code for that amino acid, which would thus be transported to its correct position on the protein template.

REFERENCES

Avery, O. T., MacLeod, C. M., and McCarty, M. (1944) *J. exp. Med.*, **79**, 137.

Brenner, S., Benzer, S., and Barnett, L. (1958) *Nature, Lond.*, **182**, 983.

Brown, G. L. (1960) In: Microbial Genetics. Symposium of the Society for General Microbiology, No. 10. Cambridge; p. 208.

Crick, F. H. C., Griffiths, J. S., and Orgel, L. E. (1957) *Proc. nat. Acad. Sci. Wash.*, **43**, 416.

Fraenkel-Conrat, H., Singer, B., and Williams, R. C. (1957) *Biochim. biophys. Acta*, **25**, 87.

——, and Williams, R. C. (1955) *Proc. nat. Acad. Sci. Wash.*, **41**, 690.

FREESE, E. (1959) In: Structure and Function of Genetic Elements. Brookhaven Symposia in Biology, No. 12. New York; p. 63.
GIERER, A., and MUNDRY, K. W. (1958) *Nature, Lond.*, **182,** 1457.
——, and SCHRAMM, G. (1956) *Nature, Lond.*, **177,** 702.
HERSHEY, A. D., and CHASE, M. (1952) *J. gen. Physiol.*, **36,** 39.
INGRAM, V. M. (1957) *Nature, Lond.*, **180,** 326.
LITMAN, R. M., and EPHRUSSI-TAYLOR, H. (1959) *C.R. Acad. Sci. Paris*, **249,** 838.
MESELSON, M., and STAHL, F. W. (1958) *Cold Spr. Harb. Symp. quant. Biol.*, **23,** 9.
WATSON, J. D., and CRICK, F. H. C. (1953) *Cold Spr. Harb. Symp. quant. Biol.*, **18,** 123.

DISCUSSION

In reply to questions, by **Professor N. H. Martin** and **Dr. B. W. Lacey,** about how the secondary and tertiary structure of protein molecules might be determined, **Dr. Hayes** said he thought that the specific folding of polypeptide chains, which determined the final shape of the molecules, might simply be a function of amino-acid sequence; the side-chains of particular amino acids, in particular positions in relation to other amino acids, might determine cross-linkages, which would produce bends, joining the straight α-helices. At present this seemed the most economical hypothesis whose correctness must await further progress in high resolution X-ray diffraction analysis of protein molecules.

In reply to a further question on the species specificity of DNA, and what might happen if the DNA of one species were transferred to the cells of another, **Dr. Hayes** said that, even among the bacteria, the DNA base ratio [i.e. the ratio (adenine + thymine) : (guanine + cytosine)], although constant for any one species, might vary from 0·4 to 2·0 between different species. The significance of this was not yet known. In general, it seemed that genetic homology required similar base ratios. For example, the DNA of temperate bacterial viruses, which could lysogenize their host cells and mate with the host chromosome, seemed to have the same base ratios as their hosts; on the other hand, the base ratios of some virulent bacterial viruses differed from those of the host DNA. Such viruses, although able to utilize and direct their hosts' biochemical system, lacked genetic homology.

Serum Anti-nuclear Factor and Auto-immunity

By E. J. HOLBOROW, M.D.

Taplow

Immunological studies during the last few years have repeatedly shown that the serum in systemic lupus erythematosus (S.L.E.) often contains one or more apparent antibodies reacting specifically with cell constituents of nuclear or cytoplasmic origin. These findings have strengthened the view that S.L.E. is an auto-immune disease with which other phenomena may occur, such as a positive Coombs test, thrombocytopenic purpura and leukopenia, which also seem to express the general tendency of patients to form antibodies against certain elements in their own tissues.

Among these auto-immunological phenomena the L.E. cell test stands out because it is positive at some stage in nearly every case of the disease. The L.E. cell phenomenon is mediated primarily by a serum factor which is found in the gamma-globulin fraction, and has been shown many times to be capable of acting not only on the patient's own leucocyte nuclei but also on those in normal blood. Three or four years ago, Dr. D. M. Weir and I decided to examine the serum of S.L.E. patients for a globulin with affinity for cell nuclei, using the Coons' (Coons and Kaplan, 1950) fluorescent antibody method, and to study not only blood cells but also cell nuclei in tissue sections.

Nowadays many people are familiar with Coons' method. Unfixed tissue sections are cut from a frozen block of tissue in a cryostat at −20° C, and thawed on to a slide. The section is covered with an L.E.-cell-positive serum, incubated for half an hour and washed in saline. Where an uptake of globulin by the cell nuclei has occurred (presumably due to a specific immunological reaction) this globulin may be visualized by treating the section with a Coombs antiglobulin serum conjugated with fluorescein isocyanate or isothiocyanate. A further specific reaction takes place between the now fixed L.E. globulin and the conjugated antiglobulin; under ultraviolet microscopy the sites of fixation of the L.E. globulin are shown by an apple green fluorescence. When sections are treated with normal serum no fluorescence is seen. We have chosen human thyroid as our standard substrate tissue because of the orderly arrangement of the cell nuclei which makes it easier in borderline cases to determine whether or not there is nuclear "staining". Nuclear staining may also be shown in other tissues, such as kidney, and on white cell smears. With the latter, however, we are unable to obtain satisfactorily reproducible results, probably because of variation in the quality of the smears.

Our first interest was to see how the anti-nuclear factor (A.N.F.) correlated with the presence of a positive L.E. cell test. Among 59 S.L.E. sera tested 58 were from patients positive for L.E. cells at the time, and they all gave positive A.N.F. staining. One negative was

also negative in the L.E. cell test. By contrast, over 100 normal and miscellaneous sera from general hospital cases have all been negative for A.N.F. staining. The S.L.E. sera usually give very bright staining, and some when titrated give titres of over 100, but in a few the staining has been moderate to poor. In general, sera positive for L.E. cells have also been positive for A.N.F., with two or three exceptions.

With other related diseases which were possibly in the auto-immune category, the converse was far from true, and we found that sera from cases negative for L.E. cells may be positive for A.N.F.

Drs. A. Scott and E. G. Rees of the Skin Department of St. Bartholomew's Hospital have kindly sent sera from some of their cases of discoid lupus, without systemic involvement and without L.E. cells. So far 68 of these sera have been tested, 10 of which have proved to have anti-nuclear factor.

Dr. Weir has now investigated 114 cases of rheumatoid arthritis which have been seen at Taplow and which conform with the diagnostic criteria of the American Rheumatism Association. Of these, 86 were tested for L.E. cells and 3 were positive. In all of the 114, 12 had positive A.N.F. tests. Among the 3 L.E.-cell-positive sera, 2 were A.N.F. positive and 1 negative. Among 98 cases of Still's disease (53 tested for L.E. cells, with one positive), sera from 13 were positive for A.N.F. There appear to be no definite features which distinguish A.N.F.-positive from A.N.F.-negative rheumatoid arthritis, although Dr. Weir has found a significant correlation between A.N.F.-positive tests and anæmia. Apart from the meaning of this test in rheumatoid arthritis these results suggest that the L.E. cell factor and the anti-nuclear serum factor are not identical, especially as A.N.F. is not always found in L.E.-cell-positive sera.

With Drs. D. Doniach and I. M. Roitt of the Middlesex Hospital and Dr. W. Hijmans of Leiden we have so far investigated 110 cases of Hashimoto's disease. Of these 84 are classifiable as "uncomplicated" Hashimoto's disease, with thyroid antibodies detected by the tanned cell agglutination test, by precipitation or by complement fixation, and without other abnormal findings. In this uncomplicated group there was a low incidence of A.N.F.—4 out of 84.

The remaining 10 A.N.F.-positive sera came from cases with other features additional to Hashimoto's disease, although all but 2 had the characteristic specific anti-thyroid antibodies (Table I). Of the 3 cases of systemic lupus co-existing with Hashimoto's disease 2 gave both L.E. cells and A.N.F. staining—the third had had L.E. cells in the past, but not at the time of the investigation, when the A.N.F. test was also negative. 2 apparently uncomplicated cases of Hashimoto's disease with positive A.N.F. are included in Table I because in neither were antibodies to thyroid demonstrable by the tanned-red-cell or complement-fixation tests. The incidence of positive anti-nuclear factor in the complicated group was considerably higher—10 out of 26—than in the uncomplicated group, but it is not yet clear whether this justifies placing A.N.F.-positive thyroiditis cases in a group manifesting signs of more generalized auto-immunity.

TABLE I.—HASHIMOTO'S THYROIDITIS
(Drs. Doniach and Roitt's cases)

	Total No.		A.N.F. positive	
Uncomplicated	84		4	
Complicated:				
Thyrotoxicosis	14		2	
Rheumatoid arthritis	2		0	
Cirrhosis	2		1	
Multiple sclerosis	1		1	
Urticaria	1	26	1	10
Depressive	1		1	
S.L.E.	3		2	
Tanned-red-cell test / Complement-fixation test Neg.	2		2	

Thus it seems reasonably certain that serum anti-nuclear factor, as detected by the Coons' technique, both has a wider specificity than the L.E. cell test and is, or can be, distinct from it.

As to the component or components involved at a cellular level in the anti-nuclear reaction, our attempts to define them do not so far lead to any definite conclusion. The nuclear staining reaction can be obtained with any human or, it seems, any animal somatic tissue, including the nucleated red cells of chickens and toads. The absorption of serum with calf thymus nucleo-protein removes the anti-nuclear factor, but rather large quantities have to be used—about 10 mg of nucleo-protein per ml of serum. DNA does not absorb the factor, and although histone does we have had difficulty in demonstrating that histone specifically removes A.N.F. without also removing other antibody globulins. In A.N.F.-positive Hashimoto sera, for example, in removing the anti-nuclear factor staining with histone we have also taken out the thyroid staining that is usual with anti-thyroid antibodies (Holborow *et al.*, 1959). However, other evidence points to histone as an essential component in the reaction. The first is the observation that mature spermatozoa do not take up the anti-nuclear factor (Holborow and Weir, 1959). Vendrely *et al.* (1957) have shown that in the nucleo-protein of mature mammalian sperm protamine replaces the histone present in the spermatogonia and other immature forms, which resemble somatic cells in this respect. The failure of mature sperm to stain with A.N.F., therefore, may be due to the absence of histone in their nucleo-protein, since

immature germ-cells stain very well. However, it is also possible that the cell-membrane of sperm heads is not permeable to A.N.F. Our attempts to demonstrate nuclear staining of sperm heads pre-treated with various enzymes have been unsuccessful.

The other evidence with regard to histone comes from a study, which Dr. Weir and I have made, of the effect of deoxyribonuclease (DNAse) on A.N.F. staining (Table II). If we treat

TABLE II.—DNASE EFFECT ON A.N.F. STAINING

		Nuclear staining	
		Fluorescence	Feulgen
Sections treated with:			
(1) DNAse *before* A.N.F. sera		All neg.	All neg.
(2) DNAse *after* A.N.F. sera.			
Sera from	S.L.E.	8/8 pos.	8/8 neg.
	Rheumatoid arthritis	4/5 pos.	5/5 neg.
	Hashimoto's disease	2/2 pos.	2/2 neg.
	Cirrhosis	2/2 pos.	2/2 neg.
	Still's disease	1/1 pos.	1/1 neg.
	Total	17/18 pos.	18/18 neg.

an unfixed tissue section with DNAse before treatment with A.N.F. serum and conjugated anti-globulin, no nuclear staining results because the DNA has been removed, as shown by the negative Feulgen stain. If, however, we treat a section with A.N.F. serum first and then with DNAse, and go on to stain with anti-globulin conjugate, nuclear staining persists, even though the Feulgen staining is again negative. Thus removal of the DNA does not release A.N.F. from combination with the nucleus. This again seems to point to the involvement of histone.

In repeated attempts to immunize rabbits and guinea-pigs with nucleo-protein, with and without adjuvant, intradermally and subcutaneously, we have not been able to detect an immunological response specific for nucleo-protein by skin testing, anaphylaxis, complement fixation or anti-nuclear staining.

In summary, a serum factor (or factors) present in S.L.E. is also found, though much less frequently, in discoid lupus, rheumatoid arthritis, Still's disease and Hashimoto's disease. In S.L.E. we have an example of the production of abnormal gamma globulins—due perhaps, as Burnet (1959) suggests, to mutational change in and stimulation of antibody-forming cells. The overlap of anti-nuclear factor into the disease groups described argues the wider occurrence of a similar departure from normal immunological status.

REFERENCES

BURNET, M. (1959). The Clonal Selection Theory of Acquired Immunity. Cambridge; p. 139.
COONS, A. H., and KAPLAN, M. H. (1950) *J. exp. Med.*, **91**, 1.
HOLBOROW, E. J., BROWN, P. C., ROITT, I. M., and DONIACH, D. (1959) *Brit. J. exp. Path.*, **40**, 583.
——, and WEIR, D. M. (1959) *Lancet*, i, 809.
VENDRELY, R., KNOBLOCH, A., and VENDRELY, C. (1957) *Exp. Cell. Res.*, **13** (suppl. 4), 279.

DISCUSSION

In reply to questions, **Dr. Holborow** said he concluded that the L.E. cell factor and the anti-nuclear factor were separate. On the point of non-specific staining in fluorescent-antibody work he recommended the use of Kaplan's method (*J. Immunol.*, 1958, **80**, 254) of absorbing anti-globulin conjugates with human tissue powder neutralized with anti-human globulin serum.

Cell Nuclei and Gamma Macroglobulins

By JOHN L. FAHEY, M.D., THOMAS E. DUTCHER, M.D. and HOWARD C. GOODMAN, M.D.
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THE relationships of cell nuclei and serum proteins have received attention only in recent years. Most of this attention resulted from the discovery that serum proteins in lupus erythematosus reacted with and caused disorganization of the cell nuclei. The far-reaching implications of this observation and subsequent developments in this field have been reviewed by Dr. Holborow (p. 13). I will now consider a group of serum proteins, known as the gamma macroglobulins, which participate in the normal functions of the body and which may reflect certain changes in disease.

The gamma macroglobulins account for about 1% of the total serum protein. They are known as gamma macroglobulins because on free electrophoresis they migrate as gamma globulins. Their molecular weights, however, are greater than those of most serum proteins, hence the term macroglobulin. Most of the gamma globulins in normal serum have a sedimentation coefficient of 6·6S, but 5 to 10 per cent have sedimentation coefficients of 18S. These are the gamma macroglobulins. The 6·6S and 18S gamma globulins can be physically separated from one another by ultracentrifugal procedures or by chromatographic procedures on columns of anion-exchange cellulose. Some of the properties of the two gamma globulin groups are collected in Table I (Müller-Eberhard *et al.*, 1956; Fahey and Horbett, 1959; Fahey, 1960).

The 18S gamma globulins of normal serum include antibody activities, of which the iso-hæmagglutinins are the best known. Gamma macroglobulin levels are altered in a number of diseases. The most marked increases are seen in Waldenström's macroglobulinæmia (Waldenström, 1944) and severe reductions of

TABLE I.—COMPOSITION OF GAMMA GLOBULIN (6·6S) AND GAMMA MACROGLOBULIN (18S) GROUPS

	Gamma globulin	Gamma macroglobulin
Ultracentrifugal sedimentation coefficient ..	6·6S	18S
Molecular weight ..	160,000	1,000,000
Hexose content	1–2%	5–6%
Antigenic properties ..	Apparently uniform	Additional distinct component
Antibody activities ..	Mumps virus Influenza virus Typhoid "H" *Histoplasma capsulatum* L.E. cell factors	Isohæmagglutinins Rh (Anti-D,C) factors Typhoid "O" "Rheumatoid factor" Certain L.E. serum antinuclear activities

18S gamma globulin may be seen in chronic lymphocytic leukæmia or multiple myeloma. The finding of disease-specific activities within the 18S gamma macroglobulins is of particular interest. The "rheumatoid factor", for instance, is an 18S gamma globulin (Franklin *et al.*, 1957).

Serological Activity in Lupus Erythematosus

Until recently, the serum anti-nuclear factors were thought to be among the smaller 6·6S gamma globulins. The recognition that 18S gamma macroglobulins might react with cell nuclei came about from studies of the serum factors in lupus erythematosus that reacted with nucleo-protein preparations. Goodman (1959) noted that sera of some patients with lupus erythematosus reacted strongly with nucleo-protein extracts prepared from liver, but weakly with nucleo-protein extracts from the thymus. We studied these anti-liver nucleo-protein factors in some detail and found them to be gamma macroglobulins, that is, within the group of gamma globulins with a molecular weight about 1,000,000 and an ultracentrifugal sedimentation coefficient of 18S (Goodman *et al.*, 1959). This finding was unexpected for the serum factors responsible for L.E. cell formation and, in fact, every other serological reaction in lupus erythematosus had been described as being a property of the smaller, 6·6S gamma globulins with molecular weight of about 160,000 (Holman and Robbins, 1959). Why some patients with lupus erythematosus produce the large molecule antibody to nucleo-protein instead of the smaller, more typical antibodies with molecular weight of about 160,000 remains unknown. Similarly, why the isohæmagglutinins or many Rh antibodies should be large molecular weight antibodies is still to be answered.

Site of Macroglobulin Formation

Very little is known of the factors controlling production of the gamma macroglobulins and it is only recently that the site of origin of these interesting proteins has been considered. We have approached the problem from two standpoints. First, the cellular changes of diseases characterized by markedly increased gamma macroglobulins were examined. Second, we attempted to identify gamma macroglobulin within the tissues by means of immunofluorescent techniques.

Markedly increased gamma macroglobulin is an essential and, probably, unique feature of the disease known as Waldenström's macroglobulinæmia, and the morphologic changes in this disease should be of help in characterizing the cells of macroglobulin origin. Examination of the lymph nodes or bone-marrow of a patient with such marked serum protein changes reveals marked increases in lymphocytes or lymphoid plasma-cells. The lymphocytoid plasma-cells show the eccentric nucleus, paranuclear clear zone and deeply basophilic cytoplasm of the plasma cell, but the nuclear chromatin pattern more nearly resembles that of a lymphocyte. These lymphocytoid-plasma cells are of additional interest because some contain discrete collections of intranuclear and intracytoplasmic material which stain pink or red with Giemsa stain (Dutcher and Fahey, 1959). Other stains confirm the protein nature of the intranuclear material.

Intranuclear Glycoprotein in Macroglobulinæmia

The intranuclear and intracytoplasmic protein collections were notable also for having a high carbohydrate content which was revealed by a strong PAS staining reaction (Dutcher and Fahey, 1959). The significance of the relatively high carbohydrate content, we felt, lay in the indication that this intracellular, intranuclear glycoprotein might well be identical with the circulating macroglobulin. Gamma macroglobulins also contain a relatively large amount of carbohydrate. If spread on a glass slide they stain with the same intensity as is seen within the lymphocytoid plasma-cells.

Additional evidence of identity between the intracellular glycoprotein and the circulating macroglobulin was obtained by immunofluorescent techniques. Antisera to macroglobulin, prepared in rabbits and absorbed so as to be specific for the gamma macroglobulin, were labelled with isothiocyanate. Bone-marrow preparations from patients with macroglobulinæmia treated with the specific antisera reacted to show intracellular, frequently intranuclear, fluorescent staining (Dutcher and Fahey, 1960). On counterstaining, these areas were found to be PAS positive. This evidence strongly supports the idea that the intranuclear material was gamma macroglobulin.

The finding of large amounts of macroglobulin within the lymphocytoid plasma-cell is compatible with the postulate that these cells synthesize gamma macroglobulin. The cytoplasm appears

to be involved in gamma macroglobulin formation since the immunofluorescent studies show that there may be considerable amounts of macroglobulin in the cytoplasm, and the cytoplasm of the lymphoid-plasma cells is known to be rich in ribonucleoprotein and endoplasmic reticulum as are all other cells producing quantities of protein for extracellular distribution. The finding of gamma macroglobulins within the nucleus raises the possibility that some macroglobulins are formed in the nucleus, although the presence of macroglobulin within the nucleus does not prove that it is formed within the nucleus, or even within the cell. However, examination of morphologic material from patients with macroglobulinæmia suggests progressive increase of the macroglobulin collection within the nucleus and eventual passage into the extracellular fluid (Dutcher and Fahey, 1959).

The finding of intranuclear macroglobulin may signify an increased production of gamma macroglobulin. It is conceivable that the intranuclear 18S gamma globulin collections are analogous to the Russell bodies containing 6·6S gamma globulin in plasma-cell cytoplasm. Intranuclear gamma globulin localization is not restricted to cells which are malignant. White (1961) at the London Hospital has shown that antibodies may be present in the nucleus of germinal follicle cells and medullary plasma-cells of lymph nodes from hyperimmunized rabbits. We have also seen intranuclear PAS-positive material in lymphoid cells of a few patients without Waldenström's macroglobulinæmia. Cells with intranuclear PAS positive material, however, have not been found in patients with multiple myeloma or lymphocytic leukæmia. Recognition of these cells has proved to be of some value in suggesting the diagnosis of Waldenström's macroglobulinæmia, but they probably also occur in other diseases with reactive or secondary macroglobulin increases.

These observations emphasize several aspects of the relationship between cell nuclei and gamma macroglobulins. More facets of this relationship will become apparent with the extension of morphologic, immunological and physicobiochemical approaches to the study of cell function in health and disease.

REFERENCES

DUTCHER, T. F., and FAHEY, J. L. (1959) *J. nat. Cancer Inst.*, **22**, 887.

——, —— (1960) *Proc. Soc. exp. Biol., N.Y.*, **103**, 452.

FAHEY, J. L. (1960) *Science*, **131**, 500.

——, and HORBETT, A. P. (1959) *J. biol. Chem.*, **234**, 2645.

FRANKLIN, E. C., HOLMAN, H. R., MÜLLER-EBERHARD, H. J., and KUNKEL, H. G. (1957) *J. exp. Med.*, **105**, 425.

GOODMAN, H. C. (1959) *Clin. Res. Proc.*, **7**, 264.

——, FAHEY, J. L., MALMGREN, R. A., and BRECHER, G. (1959) *Lancet*, ii, 382, and unpublished observations.

HOLMAN, H., and ROBBINS, W. (1959) *Arthr. & Rheum.*, **2**, 468.

MÜLLER-EBERHARD, H. J., KUNKEL, H., and FRANKLIN, E. (1956) *Proc. Soc. exp. Biol., N.Y.*, **93**, 146.

WALDENSTRÖM, J. (1944) *Acta med. scand.*, **117**, 216.

WHITE, R. G. (1961) *Scientific Basis of Medicine: Annual Reviews* (in press).

DISCUSSION

Dr. E. J. Holborow asked whether it was possible to prepare rabbit antisera to normal gamma macroglobulin, or whether only abnormal macroglobulins were immunologically distinct from 6·6S gamma globulins.

Dr. J. L. Fahey, in reply, said that antisera had been prepared to normal 18S gamma globulins and to 18S gamma globulins from patients with macroglobulinæmia. These antisera, when reacted with purified gamma macroglobulins in an Ouchterlony double diffusion agar plate show at least two distinct precipitin lines. One of these is characteristic of 6·6S gamma globulins, the other for 18S gamma globulins. The 6·6S and 18S gamma globulins appear to share many antigens in common, but each type of protein also seems to have distinctive antigenic characteristics. Thus, an antisera can be absorbed with 6·6S gamma globulin so that it will no longer react with 6·6S gamma globulin, but will continue to react with 18S gamma macroglobulins. Whether all of the 18S proteins have distinct characteristics from the 6·6S gamma globulins or whether all 18S gamma macroglobulins normally possess identical antigenic characteristics is not known.

Professor J. V. Dacie asked whether Dr. Fahey had any evidence that 18S globulins in macroglobulinæmia had any specific immunological characters?

Dr. J. L. Fahey replied that they had no evidence that the macroglobulins had characteristics not present among the normal gamma macroglobulins. It was not surprising they were different from the 6·6S proteins, but he did not know of any conclusive proof that they had antigenic components not present within the group of normal 18S gamma macroglobulins. In any event they were closely related to the normal proteins.

Dr. B. W. Lacey said that it would now seem imperative to attempt to dissect the 18S component, by Porter's methods or other means, in order to analyse the basis of its specificity.

Dr. J. L. Fahey replied that they were working at the present time on several related proteins which should help to elucidate the subdivisions of gamma macroglobulins. One problem would be to relate the findings with macroglobulinæmic macroglobulins to the normal gamma macroglobulin which were difficult to obtain in a pure state. He certainly agreed, however, with the importance of dissecting the gamma macroglobulins in an effort to understand their special characteristics.

BOOKS RECEIVED FOR REVIEW

Alexander (G. L.), and **Norman (R. M.).** The Sturge-Weber syndrome. pp. vii+95. Bristol: John Wright. 32s. 6d. 1960.

Bourne (J. G.). Nitrous oxide in dentistry. Its danger and alternatives. pp. x+181. London: Lloyd-Luke. 30s. 1960.

British National Formulary 1960. Alternative ed. pp. 292. London: Pharmaceutical Press and B.M.A. 8s. 1960.

Brouha (L.). Physiology in industry. Evaluation of industrial stresses by the physiological reactions of the worker. International Series of Monographs on Pure and Applied Biology. Volume 4 of Modern Trends in Physiological Sciences. pp. xii+145. Oxford, &c.: Pergamon Press. 40s. 1960.

Buie (L. A., Sr.). Practical proctology. 2nd ed. pp. xvi+737. Springfield, Ill.: Thomas. Oxford: Blackwell. £9. 1960.

Bulloch (W.). The history of bacteriology. pp. xii+422. London: Oxford University Press. 30s. 1960. (First printed in 1938.)

Burckhardt (W.). Atlas and manual of dermatology and venereology. Translated and edited by Stephen Epstein. pp. xiii+276. London: Baillière. 112s. 1959.

C.I.O.M.S. The transparency of the cornea. A Symposium organized by the Council for International Organizations of Medical Sciences. Edited by Sir Stewart Duke-Elder and E. S. Perkins. pp. xii+268. Oxford: Blackwell. 45s. 1960.

Crow (W. B.). A synopsis of biology. pp. xv+1056. Bristol: John Wright. 90s. 1960.

Davis (L.). Fellowship of surgeons. A history of the American College of Surgeons. pp. vi+523. Springfield, Ill.: Thomas. Oxford: Blackwell. 84s. 1960.

Dental Practitioners' Formulary 1960. pp. 54. London: Pharmaceutical Press. 3s. 6d. 1960.

Ehrlich (P.). The collected papers. In four volumes including a complete bibliography. Edited by F. Himmelweit. Vol. II. Immunology and Cancer Research. pp. viii+562. Vol. III. Chemotherapy. pp. viii+615. London, &c.: Pergamon Press. £8 each vol. Vol. II, 1957; Vol. III, 1960.

Essex-Cater (A. J.). A synopsis of public health and social medicine. pp. xii+563. Bristol: John Wright. 55s. 1960.

Gray (L. A.). A textbook of gynecology. pp. xv+470. Springfield, Ill.: Thomas. Oxford: Blackwell. £6 4s. 1960.

Greenberg (D. M.), and **Harper (H. A.),** eds. Enzymes in health and disease. pp. xvi+459. Springfield, Ill.: Thomas. Oxford: Blackwell. £5 16s. 1960.

Hurley (H. J.), and **Shelley (W. B.).** The human apocrine sweat gland in health and disease. American Lecture Series No. 376. pp. x+138. Springfield, Ill.: Thomas. Oxford: Blackwell. 52s. 1960.

Jones (M. S.). An approach to occupational therapy. A survey based on the observation of 4,115 patients treated in Farnham Park Recuperative Home, October 1947 to December 1955. pp. xv+245+14. London: Butterworth. 42s. 1960.

Kulowski (J.). Crash injuries. The integrated medical aspects of automobile injuries and deaths. pp. xlii+1080. Springfield, Ill.: Thomas. Oxford: Blackwell. £13. 1960.

Mayo Clinic and Mayo Foundation. Collected papers of the Mayo Clinic and Mayo Foundation. Vol. 51, 1959. pp. xv+825. Philadelphia and London: Saunders. £4 18s. 1960.

Queen Square and the National Hospital. 1860–1960. With a foreword by Sir Ernest Gowers. pp. x+112. London: Arnold (for the Chartered Society of "Queen Square"). 30s. 1960.

Sarwer-Foner (G. J.), ed. The dynamics of psychiatric drug therapy. pp. xxviii+624. Springfield, Ill.: Thomas. Oxford: Blackwell. £6 8s. 1960.

Seymer (L.). Florence Nightingale's nurses. pp. xi+169. London: Pitman. 20s. 1960.

Shaw's Textbook of Operative Gynæcology. Revised by John Howkins. 2nd ed. pp. viii+484. Edinburgh and London: Livingstone. £5 5s. 1960.

Smithers (D. W.). A clinical prospect of the cancer problem. Introductory volume of neoplastic disease at various sites. pp. xv+232. Edinburgh and London: Livingstone. 37s. 6d. 1960.

Society for Endocrinology. Quantitative paper chromatography of steroids. Proceedings of a conference held at the Ciba Foundation, London, on July 1, 1958. Edited on behalf of the Society for Endocrinology by D. Abelson and R. V. Brooks. Memoir No. 8. pp. vii+103. Cambridge: The University Press. 30s. 1960.

Sorsby (A.), and **Ungar (J.).** Antibiotics and sulphonamides in ophthalmology. pp. ix+117. London: Oxford University Press. 12s. 6d. 1960.

Spencer (R. P.). The intestinal tract. Structure, function and pathology in terms of the basic sciences. pp. xvii+411. Springfield, Ill.: Thomas. Oxford: Blackwell. £5 2s. 1960.

Section of Orthopædics

President—DAVID TREVOR, M.S.

Meeting
March 1, 1960

SYMPOSIUM ON THE EARLY MANAGEMENT OF SOFT TISSUE INJURIES OF THE EXTREMITIES

Mr. Rainsford Mowlem (London):

Skin and Supporting Tissues

Early efficient treatment of injuries may make all the difference between complete recovery in a few weeks and persistent disability after months of surgical endeavour. "Minor surgery" has no place in this context as preservation of function often depends on early major surgical decisions.

Although the subject is that of injuries of the extremities, I intend to spend more time in dealing with the hand and the arm than with the leg. The hand is of course more frequently hurt. It is also an extremely specialized projection of the cortex—both sensory and motor.

An early appraisal of the injury is essential. Bony injury, loss of skin cover, loss of motor function, loss of sensation and interruption of the vascular supply must all be looked for. The most urgent is of course interference with blood supply or venous drainage. Vascular failure may develop some time after the injury; the persisting displacement of a fracture may so angulate a blood vessel as to occlude it; the deep hæmatoma may slowly increase until it causes a tourniquet effect; the damage round a vessel may cause an occlusion from spasm or pressure, which if untreated will result in the disaster of a Volkmann's contracture. These perils can be avoided only if the possibility of an insidious onset is remembered and a constant survey is made of the colour, temperature, mobility and sensation of the affected limb.

Early immobilization of a fracture is essential to reduce these risks and to avoid further damage, but this immobilization need not always be definitive. The most immediate problem may well be the reduction of swelling and consequent diminution of skin tension. Gravity is by far our greatest ally and coolness is the next. A few days spent in elevation will often work wonders but there should be no hesitation in surgical decompression if it appears desirable. A delay of a few days in the restitution of intact skin cover is not important if adequate precautions are taken.

The next most urgent problem is loss of skin. So long as the surface epithelium is broken there exists the risk of infection. Intact skin is a much more efficient protection than is an "antibiotic umbrella".

Incised wounds demand early and accurate suture, unless there is an underlying œdema due perhaps to a comminuted fracture and an extravasation of blood rendering the limb so tense that skin closure would produce a tourniquet effect. Even then, if the wound exposes a tendon, a bone, a joint cavity or a fracture line, closure is essential, although a relaxation incision in a less vulnerable area may be an immediate necessity. In such a case a split skin graft can be cut at operation and stored in the ward refrigerator so that it is available for application at the first post-operative dressing, by which time the immediate risk will have subsided.

Losses of skin and subcutaneous tissue causing similar exposures of vulnerable structures may necessitate the immediate importation of flaps from elsewhere, either from the same limb, from its fellow or from the trunk. Flaps from the same limb are always difficult to arrange but the least satisfactory is the so-called "strap flap" which naturally evolves after the use of a "relaxation" incision. Unless the patient is very thin and the flap exceptionally well placed and designed, the end-result is tension and some breakdown at the very point where protection is needed. It is generally better to design a flap which can be transposed to give cover and to rely on free-grafting the area from which it comes.

Avulsed or stocking flaps are commonly the result of run-over injuries. The flap is torn down at the fascial plane, but remains adherent to the limb. It is all there and the tendency to replace it is almost overpowering. There are times when that is the right thing to do, but more often the flap is so bruised that it cannot survive. There is no bleeding from its edges and no evidence of a cutaneous blood supply except near its base. The intravenous injection of dyes into the circulation does not result in staining of the flap and such a method can be used to determine which areas are still viable. It is more usual to trim the flap back until the marginal bleeding indicates viability. The defect can be

covered by split grafts which can be immediately applied or else left in store for a few days until the recipient area is cleaner and less contused.

In the *injured hand* the applications of the principles mentioned above become increasingly urgent, for the mechanism of the hand is so complex that minor infection or persistent œdema may cause havoc. Failure to elicit a movement when examining the hand does not always mean motor loss. Pain may be sufficient to cause inhibition. Neither does limited movement, say of a terminal phalanx, always mean that the flexor profundus is intact. The more proximal the lesion, for example at the wrist, the less specific is the apparent loss of mobility. Loss of sensation due to the division of only one digital nerve is difficult to evaluate but it is there. The probabilities of damage must be remembered and allowed for.

In assessing any injury and determining its correct line of treatment there are many factors to be considered. Careful examination must of course include the injured area, but the patient's age, health, employment and skill are also important.

A long-term repair programme may well be indicated to save or replace the traumatized region in a young man with special skills, whilst a similar lesion in an elderly pensioner would be better treated by amputation. Surgery should not be advised without due thought as to the end-result and the time taken to achieve it. To rebuild a digit can mean the restitution of earning power but it can also mean the creation of a useless structure at the expense of so many weeks in hospital that all inclination to return to work has been lost. Each injury presents an individual problem.

The inevitable sequel to almost every injury, whether there be skin loss or not, is swelling. This may constitute a risk to circulation, particularly on the forearm, which can be countered only by immediate surgery to expose the main vessels concerned. There are few conditions so irremediable as an established Volkmann's contracture and it is a condition which can under most circumstances be avoided or at least minimized.

More frequently œdema inflates the whole hand so that its bulk is increased by 20% or more. The fingers are splinted by swelling of their subcutaneous tissue, the tendon sheaths and joints are full of fluid. This fluid, if allowed to persist, will inevitably be replaced by fibrous tissue and its early removal becomes a matter of primary and urgent concern.

Support, elevation and cooling are the lines of attack. Support is provided to maintain the fingers and wrist-joints in a neutral position and is best achieved by a plaster of Paris slab on the palmar surface, maintaining the wrist in the mid-position and the finger-joints each flexed to about 45 degrees. The thumb is abducted. The position as a whole is similar to that necessary to grasp a cricket ball. It is difficult to obtain and more difficult to maintain.

The whole arm is elevated so that the shoulder is its lowest point. If exposure and cooling are available so much the better. Movement is encouraged only as it becomes relatively effortless. This regime is continued for at least four days and is indicated in almost every hand injury, closed or open, operated upon or not operated upon.

Wounds fall into two groups—the tidy and the untidy (Rank and Wakefield, 1953, Surgery of Repair as Applied to Hand Injuries. Edinburgh and London).

The *tidy* are capable of being sutured to restore an intact skin surface. For limited lesions local anæsthesia is adequate but to embark on a repair which may end by being a tendon graft under such an anæsthetic is undesirable. Neither is local anæsthesia indicated in the nervous or the very young. Again the assessment must take into account both the injury and the patient.

A thorough cleansing with Cetavlon is followed by exploration of the wound to ensure that there is no deep damage before closing the skin defect. Severed digital nerves are sutured immediately and tendon repair may be carried out. Immediate suture is the rule at the wrist and proximal parts of the palm and, under some circumstances, the distal 1 to 1·5 cm of the flexor profundus and of the flexor longus pollicis. Elsewhere, i.e. when both tendons are involved within their sheaths, repair is usually deferred, though under ideal circumstances an immediate tendon graft is possible.

Skin losses which expose tendon, bone or joint cavity should be repaired by flaps which can often be derived from an adjacent finger, from the dorsum of the hand or from the proximal part of the palm. Such a flap is designed to transpose the defect to a point where it can be adequately covered by a split skin graft whilst the imported tissue, having its own blood supply, protects the underlying avascular structures from infection.

If such a flap is not available on the hand, the opposite arm is the most likely place to find one and failing that the trunk may be used. The texture of such a flap remains always that of the area from which it came, while its sensibility, if any, must depend on the integrity of a nerve supply in the area into which it is imported.

Untidy lesions mainly result from injuries in machinery. The hand and all its structures are lacerated. The greatest experience is necessary to decide what to try to preserve and what to remove. This may well be conditioned by the patient himself. The clothing of fingers by tubes of skin, however exciting as a surgical exercise, is seldom rewarding. A short finger is better than a stiff, painful, or perhaps anæsthetic digit encased in scar or skin graft, but every millimetre of an injured thumb is worth preserving.

Heat burns and electrical burns are a special problem, but they are associated with the same difficulties—early severe œdema and skin losses sometimes exposing tendons or joints. The treatment of the œdema is urgent, the restoration of the skin lesion is less urgent, provided infection can be avoided.

No two hand injuries present exactly the same difficulties. Their early recognition and treatment in the right order of priority demands considerable thought but is more than usually rewarding in the restoration of function to a mechanism both complex in its nature and essential in its function.

Professor Charles Rob (London):

Vascular Injuries

In this paper I shall deal only with injuries to large and medium sized arteries. I shall omit small vessel and capillary injuries, particularly such lesions as frost-bite and immersion or trench foot. The usual result of an arterial injury is hæmorrhage which must be controlled, but closed injuries often cause thrombosis and several less common complications which will also be discussed. Hæmorrhage is usually controlled by a pressure dressing, occasionally a tourniquet or emergency ligature may be required.

Management of Acute Arterial Occlusion

There are few emergencies in medical or surgical practice which are influenced to a greater extent by good initial medical care than sudden occlusion of the main artery to a limb. The first few hours are of great importance, simple measures taken at once whilst the patient is awaiting transfer to hospital serve to minimize the effects of such a lesion.

Reduction of metabolic needs.—This is best achieved by keeping the limb cool. Rest further reduces the metabolic needs. Rest may also be encouraged by the relief of pain. It is very important not to elevate the limb: it should be placed horizontal or slightly dependent.

Development of the collateral circulation.—The most efficient way of encouraging the development of the collateral circulation is to establish reflex vasodilatation. Evidence produced by Sir Thomas Lewis and others has established that the vasodilatation produced in this way equals and sometimes exceeds that of either a sympathectomy or a sympathetic nerve block. It is also important that splints, dressings or the patient's posture should not constrict the region of vascular occlusion around which the collateral circulation must develop.

Anticoagulants have an important place in the management of patients with sudden arterial occlusion. They help to limit the extension of the thrombosis, particularly into the vessel distal to the block where the blood flow is slow. They are, of course, contraindicated if there is a large wound or major closed injury, but in many patients with closed arterial injuries they are of value. If heparin is used there is no risk of undue hæmorrhage during a subsequent surgical operation because protamine sulphate, which works in a few minutes, is an efficient antidote to the heparin.

General management includes the maintenance of an adequate blood pressure and hæmoglobin level by blood transfusion if necessary. The prevention of infection is also important. Deformities must be prevented by physiotherapy and splintage.

Operative surgery may take one of three main forms: (1) Arterial reconstruction procedures designed to restore a normal blood flow. (2) Measures to aid the establishment of an efficient collateral circulation. (3) Amputations if the procedures described above fail.

Arterial reconstruction should be the surgeon's aim in all cases of division of a main artery, that is an artery proximal to the popliteal and brachial bifurcations in the limbs. As Table I shows, in war where large numbers of arteries have to be ligated the number of amputations is high; to-day in civilian practice arterial ligature can often be avoided.

TABLE I.—AMPUTATIONS AFTER ARTERIAL INJURY IN WAR

Artery	Combined figures Makins (1919) and DeBakey and Simeone (1946) No. of patients	Amputations
Aorta	8	7 (87·5%)
Subclavian	61	10 (16·4%)
Axillary	182	37 (20·3%)
Brachial	801	171 (21·3%)
Radial and ulnar	28	11 (39·3%)
Common iliac	14	8 (57·1%)
External iliac	34	14 (41·2%)
Femoral	883	349 (39·5%)
Popliteal	646	426 (65·9%)
Anterior and posterior tibial	98	64 (65·3%)

The best method of arterial repair is end-to-end suture, lateral repair nearly always fails in patients with an arterial injury. The whole damaged segment must be removed; if end-to-end suture is impossible a graft should be inserted. A number of materials have been used as arterial

substitutes; these include homologous arterial transplants, autogenous vein grafts and plastic prostheses, of which the best have been made so far of terylene (Dacron) and Teflon. In general the plastic substitutes work well for aortic replacement but the thrombosis rate after a follow-up for as short a period as one year is high when they are used for smaller vessels. This means that for the replacement of such vessels as the femoral, popliteal and subclavian arteries an autogenous vein graft or a homologous arterial transplant is preferred. Table II gives the results which we have obtained with these materials as arterial substitutes, and Table III is a long-term follow-up. In these

TABLE II.—RESULTS OF ARTERIAL RECONSTRUCTION IN 665 PATIENTS

Operation	No. of patients	Dead	Thrombosed	Patent
Direct suture	41	3	3	35
Thrombo-endarterectomy	197	5	23	169
Autogenous vein ..	50	4	18	28
Homologous artery ..	285	20	62	203
Plastic prosthesis	92	12	23	57

TABLE III.—RESULTS IN 400 PATIENTS FOLLOWED FOR ONE AND A HALF YEARS OR LONGER

Operation	No. of patients	Dead	Thrombosed	Patent
Direct suture	20	2	2	16 (80·0%)
Thrombo-endarterectomy	97	3	8	86 (88·7%)
Autogenous vein ..	29	2	14	13 (44·8%)
Homologous artery ..	206	12	53	141 (68·4%)
Plastic prosthesis	48	8	10	30 (62·5%)

series the reason for operating in the majority of patients has been an arterial thrombosis due to atherosclerosis.

Complications of an arterial injury.—Apart from hæmorrhage and arterial occlusion, the following complications may follow an arterial injury: aneurysm, arteriovenous fistula, gangrene, intermittent claudication, ischæmic contracture and vascular spasm. The formation and treatment of arterial aneurysms and arteriovenous fistulæ have interested surgeons for centuries. To-day most such lesions can and should be treated by an arterial reconstruction procedure.

Mr. Guy Pulvertaft (Derby):

Tendons and Nerves

The majority of these injuries occur in the upper limb and mainly in relation to the wrist and hand; I shall confine my remarks to these regions.

Tendon Divisions

Technique of suture.—The suture material should be fine and cause the least possible tissue reaction. Mukherjee and Douglas (1951), studying the relative reactions set up in nerve tissue by nylon, terylene, human hair, silk and stainless steel wire, demonstrated clearly that wire was the only material which causes little or no reaction. It has been found in practice that there is little to choose between fine silk (No. 4/0–6/0) and wire and the choice is largely one of personal preference. It has always been my custom to use single strand wire; B.W.G. 40 for the main suture and B.W.G. 43 (No. 6/0) for auxiliary stitches. Kinking must be avoided and the wire is tied by a reef knot, the ends being cut off flush with the knot.

There is no better method for joining two tendons of equal size than the Bunnell criss-cross stitch. When many tendons require repair as at the wrist level, I use the Bunnell "double right angle stitch". For joining a small to a large tendon, e.g. the proximal end of a tendon graft, I use a special type of interlacing suture. The distal end of a graft may be attached to a tag of profundus, by the Bunnell withdrawal stitch or by passing the graft through a transverse hole bored in the terminal phalanx and stitching it back to itself. The withdrawal stitch is the neatest and passing it through the bone is the most secure.

Conditions of the wound.—It is unwise to perform primary tendon suture unless (*a*) not more than eight hours have elapsed since injury; some authorities say less; (*b*) there has not been severe contamination; (*c*) there are no complications such as severe skin loss, severe fracture or joint injuries or a general crush factor; (*d*) operative conditions are satisfactory and the correct instruments and suture material available.

Rank and Wakefield (1953) divide hand wounds into two types—the tidy and the untidy. The tidy wounds are typically produced by knives, axes and glass; they are generally clean cut, skin loss is minimal and fracture exceptional. In these cases primary tendon suture is permissible. The untidy wounds are caused by machinery, power saws and power presses; skin edges are jagged or crushed, skin loss is usual and multiple fractures are common. Primary tendon repair is not advisable.

Furlong (1957) has expressed the situation with clarity: "Like other difficult decisions, each instance must be judged separately. The decision to be content with skin suture only or to go on to primary tendon repair has to be made. The surgeon will bear in mind whether the hand is extensively and heavily contaminated before the accident; whether the cut is clean and amenable to enlargement according to surgical principles or whether it is lacerated and so contaminated as to make primary healing unlikely. Further he must consider the time-interval between trauma and surgery and finally decide whether he has sufficient skill to carry out delicate tendon surgery."

Site of injury.—Assuming that the wound conditions are favourable, the decision to use splintage only, primary suture or secondary repair, in some form or other, rests upon the site of injury.

Extensor tendons of the forearm, wrist, hand and digits.—Divided extensor tendons in the fingers and over the metacarpophalangeal joints may in many cases be treated by splintage, as retraction of the proximal end does not occur beyond the limits of positional splintage.

Division of the extensor tendon in the distal part of the finger leading to the mallet deformity is best treated by splintage of the terminal joint in extension by a pin passed across the joint from distal to middle phalanx. It is advisable to hold the proximal interphalangeal joint in flexion by external splintage.

Division of the central slip attached to the middle phalanx—the button-hole injury—is treated by external splintage holding the metacarpophalangeal and interphalangeal joints in extension.

Division over the metacarpophalangeal joint may also be treated by splintage as part of the lateral expansion is usually intact and this prevents proximal retraction.

Tendon divisions proximal to this level need to be sutured.

In the thumb, it is advisable to suture the extensor and abductor tendons at whatever level they may be divided.

Flexor tendons of the forearm, wrist, hand and digits. Thecal sheath of the finger.—Division of sublimis tendon alone requires no treatment. Division of profundus distal to the sublimis attachment may be sutured primarily. When it is divided between the distal palmar crease and the sublimis attachment, primary suture should not be done; the choice lies between arthrodesis of the terminal joint, tenodesis of the profundus tendon or restoration of profundus action by a free tendon graft, all of which are performed as secondary procedures. The decision depends upon several factors; age, state of the finger, occupation and the wishes of the patient. The operation of tendon grafting is one of some magnitude for what is a comparatively minor disability. It should not be advised unless the patient is determined to seek perfection and the surgeon is confident of his ability to offer a reasonable expectation of success without undue risk of doing harm. The sublimis tendon, if intact, is not removed.

I advise tendon grafting for the index and middle fingers in the majority of persons because of the important thumb, index and middle finger pinch. I use it for the ring and little fingers only when the patient requires this action on account of his occupation or special interests, e.g. a musician or skilled technician. For those employed in general labouring work and when a quick and certain result of a less perfect nature is desired, I believe it is better to arthrodese the terminal joint. For children it is good counsel to advise grafting as the lengthy recovery period is of no significance nor can one foretell what may be the child's later requirements.

During the years 1942–59, 34 patients were treated. One case could not be traced, but the records at nine weeks indicate that progress was good and a satisfactory result anticipated. Of the 33 cases, 4 were complete failures in that no active movement was restored. Excluding these 4 cases, 92% attained 30 degrees, or more, active movement at the distal interphalangeal joint and 55% reached to within $\frac{1}{2}$ in. or less of the distal palmar crease.

Division of both sublimis and profundus tendons within the digital theca should not, as a general rule, be treated by primary suture. "Poor results the world over follow sutures of flexor tendons in what is called 'no man's land', that is, between the distal crease of the palm and the middle crease of the finger" (Bunnell, 1956). This opinion was reached by Bunnell as the result of seeing many poor results of primary and secondary suture in this region. Most surgeons, including myself, would agree with Bunnell that the treatment of choice is primary skin suture and secondary tendon grafting, but there are a few experienced men who think otherwise. The Chicago school, Posch of Detroit, Verdan of Lausanne and Bolton of Stockport are among those who consider that there is a case for immediate suture of profundus alone when performed under ideal conditions. There are others who prefer a primary tendon graft but this I believe to be a dangerous policy because one is working in a potentially contaminated field. As Boyes (1958) says of this treatment "If you play with fire, you will eventually get burned".

Experienced surgeons can offer 75%–80% (Boyes even higher) acceptable results by tendon grafting and it does not appear that we are yet in a position to depart from the accepted teaching of skin suture and tendon graft later as a general principle.

The thumb.—Primary suture yields good results when the division has occurred in the distal part of the thumb. The less common cases of division deep in the thenar muscles may also be repaired by primary suture, but the exposure is difficult as the tendon lies in close proximity to the digital nerves and the motor branch to the thenar muscles, which, incidentally, are far more important for the thumb than is flexion action

of the terminal phalanx. The results of secondary grafting are good, offering a success rate of 85%–90%. I advise my own staff not to perform primary suture except for division distal to the metacarpophalangeal joint.

Divisions in the palm.—Tendon divisions in the palm, that is between the distal border of the flexor retinaculum and the distal palmar crease, do not present the difficulties encountered in the fingers. Immediate and secondary suture give good results, but it is better to repair profundus only as cross union may occur if both tendons are repaired, which limits the action to that of sublimis alone. When the patient is seen at a late stage it is not unusual to find that retraction of the proximal ends does not allow direct suture. This difficulty can be overcome by using a small bridge graft taken from sublimis.

Divisions at the wrist level.—It is my practice to perform primary repair of all tendons divided at the wrist, with the exception of palmaris longus. Some prefer not to repair sublimis, but I have not been troubled by cross union at this level and it seems a pity to abandon sublimis power. If the tendons are not repaired primarily, retraction follows and the gaps have to be closed by bridge grafting. The results of a carefully performed primary suture are excellent.

Nerve Divisions

The results of nerve repair depend upon: (*a*) The time-interval between the injury and the connexion of the axons with the motor end plates or the sensory nerve endings; (*b*) the apposition of good quality nerve ends without undue tension or excessive positional splintage; (*c*) the precision of orientation and suture and the avoidance of hæmatoma between the nerve ends.

Primary or secondary repair.—This is a question upon which differing views are held. I do not believe that a completely authoritative statement can be made until a large parallel series of primary and secondary sutures performed under the same conditions are investigated.

There is general agreement that the small purely sensory or motor nerves in the hand should be repaired primarily if possible and that the larger mixed peripheral nerves should be repaired at once if accidentally divided in the course of an operation.

Apart from these special cases, there are, I submit, valid arguments to support the principle of secondary suture. It is, of course, understood that the nerve ends are held together by a simple suture at the emergency operation.

(1) The nerve is rarely divided by a perfectly sharp instrument and many injuries are associated with considerable violence. It follows that some contusion or stretching of the nerve occurs which may lead to subsequent intraneural fibrosis unrecognizable at the time. This makes it difficult to estimate how much of the apparently normal nerve should be removed. There is a natural tendency at an emergency operation to be too conservative in the desire to avoid creating a problem in apposition, which would necessitate a wide exposure in the presence of possible contamination.

(2) The epineurium thickens during the few weeks after nerve division and holds the stitches better.

(3) A more precise suture is more likely to be attained during a set operation with ample time than at the end of an emergency operation during which numerous tendons have been repaired.

Reconstruction.—When such a length of nerve has been damaged that the ends cannot be brought together after adequate liberation and transposition, nerve grafting should be considered. The results, in general, of nerve grafts are not so satisfactory as suture, but they are certainly better than suture performed under a tension which demands extreme positional splintage. Of the 67 cases of autogenous nerve grafting recorded in the Medical Research Council report (Nerve Injuries Committee, 1954), 28 achieved a degree of recovery similar to that of a successful suture at the same level. The actual lengths of nerve gap beyond which it is useless to attempt a suture have been worked out and are to be found in the report.

Strange's pedicle graft (1947) should be considered when there has been extensive destruction of the median and ulnar nerves in the forearm.

In treatment of irreparable motor paralysis a great deal can be done to restore function by tendon transference. Some of the most gratifying results of hand surgery are seen in this field.

Finally, it is my belief that the surgeon should be adaptable—familiar with the different techniques and able to choose the one most favourable under the circumstances.

REFERENCES

BOYES, J. H. (1958) *J. Bone Jt. Surg.*, **40A**, 262.
BUNNELL, S. (1956) Surgery of the Hand. London; p. 713.
FURLONG, R. (1957) Injuries of the Hand. London; p. 95.
MUKHERJEE, S. R., and DOUGLAS, D. M. (1951) *Brit. J. Surg.*, **39**, 271.
Nerve Injuries Committee (1954) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 282.
RANK, B. K., and WAKEFIELD, A. R. (1953) Surgery of Repair as Applied to Hand Injuries. Edinburgh and London; p. 62.
STRANGE, F. G. St. C. (1947) *Brit. J. Surg.*, **34**, 423.

Section of Radiology

President—Professor A. S. JOHNSTONE, F.R.C.S.Ed.

Meeting
March 18, 1960

The Relative Values of Surgical Hypophysectomy and of Bilateral Adrenalectomy with Oophorectomy in the Treatment of Metastatic Breast Cancer

By MURRAY A. FALCONER, M.Ch., F.R.C.S.

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THREE years ago, before the Section of Surgery of this Royal Society, Mr. Hedley Atkins and I (Atkins, 1957; Falconer, 1957) gave a preliminary report of a study which we had started at the end of 1953 into the relative value of surgical hypophysectomy compared with bilateral adrenalectomy and oophorectomy for the treatment of advanced cancer of the breast. At that stage it appeared that hypophysectomy gave slightly superior results, but the differences were not beyond the possibilities of chance. Here Mr. Atkins and I give the results of a longer-term study which has been made in conjunction with Mr. John Hayward of the Imperial Cancer Research Fund, Dr. K. S. MacLean, the Assistant Director of the Department of Medicine at Guy's Hospital, and Mr. P. H. Schurr, my colleague at the Guy's-Maudsley Neurosurgical Unit. The various follow-up data have been compiled by Mr. J. L. Hayward and analysed statistically by Dr. P. Armitage of the London School of Hygiene and Tropical Medicine. They will indicate that surgical hypophysectomy appears to be a slightly superior procedure beyond the conventional range of probability of 0·05 (1 in 20).

Some 149 patients who had passed through the Breast Clinic at Guy's Hospital between 1937 and 1959 were studied. All were examples of breast cancer in women which had reached the stage of detectable dissemination outside the breast and the axillary lymph nodes. The majority were instances of very advanced breast cancer which had already exhausted all reasonable possibilities of further treatment by breast surgery, deep X-ray therapy to local metastases, and hormone therapy. 17 patients, however, had clinical dissemination of tumour outside the breast and axilla and were submitted to an endocrine operation without prior radiation or hormone therapy in an attempt to assess the value of these operations at an earlier stage in the disease. The number of cases in this recent and subsidiary study is still too small to make any valid conclusions.

The choice of operation in our cases was made by random selection (Atkins, 1957). Prior to this operation all patients first seen by Dr. K. S. MacLean who, not knowing which operation was to be performed, excluded any in whom he thought further surgery unjustifiable. Altogether he excluded 6 for reasons such as complete paraplegia unlikely to recover even if the carcinoma was to relent, severe dyspnœa, cardiac failure, uræmia, or personality change secondary to cerebral lesions. A further 3 patients died before they could be admitted to hospital. Of the 149 patients selected for operation by randomization, 79 have undergone bilateral adrenalectomy and oophorectomy and 70 have undergone surgical hypophysectomy by techniques described by us in our earlier communication (Atkins *et al.*, 1957). The technique of hypophysectomy used by Mr. Schurr and myself is similar to that originated by Luft and Olivecrona (1953).

After either set of operations patients have to be maintained on regular cortisone therapy, which usually is 25 mg twice daily by mouth but which in times of stress, as for example during acute intercurrent infections, may have to be increased to 150 mg per day. Hypophysectomy has a slight theoretical disadvantage in that often thyroid substance has to be given in doses of from 60 to 120 mg to prevent myxœdema, while many patients also have a transient diabetes insipidus requiring vasopressin. 6 of our first 30 patients had some degree of bitemporal hemianopia, but only 1 seriously. Probably all had unilateral anosmia on the side of operation, but only 28 noticed any change in smell. These objections to hypophysectomy are more theoretical than real, for with suitable hormone supplements patients in whom the disease remits can be kept in reasonably good health. In many instances the only change which a premenopausal woman may notice is loss of periods. No cases of cerebrospinal rhinorrhœa or of meningitis have been seen after surgical hypophysectomy, a

respect in which the operation has great advantage over transfrontal interstitial irradiation hypophysectomies (*Lancet*, 1960).

Comparison of the Two Operations

The two groups of cases, those submitted to hypophysectomy and those to bilateral adrenalectomy and oophorectomy, when analysed were approximately similar in composition as regards age distribution, site and extent of metastases, and previous experience of other forms of treatment, as one would expect when cases are chosen by random selection. Counting all deaths from whatever cause within twenty days of operation as operative deaths, the operative mortality following hypophysectomy was 3 deaths (4%) and following adrenalectomy was 7 deaths (9%). It is perhaps noteworthy that all 7 patients who died after adrenalectomy had a pulmonary metastasis, whereas only 1 of the 3 who died after hypophysectomy had such a lesion. This appears to indicate that patients with pulmonary lesions should for preference be treated by hypophysectomy which involves only one anæsthetic and not by adrenalectomy which involves a two-stage operative procedure.

All the remaining patients have since been followed up at regular one- or two-monthly intervals, and their progress checked at each examination by the method known as the Mean Clinical Value (M.C.V.) of Walpole and Paterson (1949). This method assigns a scale of values such that, if all the lesions are improving the M.C.V. is 12, if on balance the lesions are stationary, the M.C.V. is 6, and if all are deteriorating the M.C.V. is 0. The appearance of this latter value is usually followed shortly by death.

There are several ways in which a statistical comparison can be made between the two groups. The principal way in which we have done it is to average out the M.C.V. for all patients at regular four-weekly intervals after operation. In compiling these averages all surviving patients and also all patients who, had they not died, could have completed each follow-up period are included, the deceased patients each being assigned an M.C.V. of zero. We found that whereas after hypophysectomy the average M.C.V. improved, reaching an average level of 7·2 at about the third month, and then declined, after bilateral adrenalectomy the average M.C.V. fell steadily from an initial level of 6 at a rate which at first sight appeared to parallel the decline in the hypophysectomy series after the third month. The longest time of survival after bilateral adrenalectomy was fifty-three months and after hypophysectomy seventy-five months.

It might be argued, however, that hypophysectomy, although superior in its results during the first two or three months after operation, subsequently loses its efficacy at a rate proportionate to that after bilateral adrenalectomy. However, the proportions of patients surviving after hypophysectomy at three months and at twelve months were 0·812 and 0·567 respectively, compared with figures after bilateral adrenalectomy of 0·666 and 0·405 respectively. These figures give a statistical probability that hypophysectomy is a superior operation of 0·04 at the third month and of 0·05 at the twelfth month, both of which come within the conventionally accepted figure of probability of 0·05.

REFERENCES

ATKINS, H. J. B. (1957) *Proc. R. Soc. Med.*, **50**, 859.
——, FALCONER, M. A., HAYWARD, J. L., and MACLEAN, K. S. (1957) *Lancet*, i, 489.
——, ——, ——, ——, SCHURR, P. H., and ARMITAGE, P. (1960) *Lancet*, i, 1148.
FALCONER, M. A. (1957) *Proc. R. Soc. Med.*, **50**, 861.
Lancet (1960) i, 489.
LUFT, R., and OLIVECRONA, H. (1953) *J. Neurosurg.*, **10**, 301.
WALPOLE, A. L., and PATERSON, E. (1949) *Lancet*, ii, 783.

A Comparison of Adrenalectomy and Oophorectomy with Hypophysectomy in the Treatment of Advanced Cancer of the Breast

By HEDLEY ATKINS, M.Ch., F.R.C.S.

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MR. MURRAY FALCONER has stated that after five years' work we have been able to demonstrate that hypophysectomy is better than bilateral adrenalectomy with oophorectomy in the treatment of advanced cancer of the breast. It is my task to answer two questions: What do we mean by "better" and, How much better?

What Do We Mean by "Better"?

In order to answer the first question it is necessary to examine the criteria by which we assess these treatments. A properly controlled trial, from the purely scientific point of view, would have demanded that we divide our population into three groups by random selection. One group would have been left untreated, one group would have been treated by hypophysectomy and one group by bilateral adrenalectomy with oophorectomy. However, the fact that occasionally miraculous and often satisfactory

alleviation can be procured by either of these operations, made this procedure unethical and we had to be content with two groups, one treated by hypophysectomy and the other by adrenalectomy with oophorectomy.

One criterion which we adopted and which has much to recommend it is length of survival measured in this instance appropriately in months. There is no argument about length of survival, which makes it an admirable criterion. There may, on the other hand, be plenty of argument as to whether this survival has been too dearly purchased or whether the quality of the life is worth preserving and these points will be considered later.

As Mr. Murray Falconer has shown, the mortality rates of the two operations expressed as a life table are different and, at three months after the operation, this difference is significant at the 0·04 level of probability. Survival rate therefore is helpful and has something to tell us about the effects of these operations.

Survival rate, however, is a crude measure in this condition because of the protean manifestations some of which, such as brain secondaries, may be lethal and others, such as skin secondaries, may be relatively innocuous. Thus, if treatment A is meted out to patient 1 with brain secondaries and this treatment is successful for three months after which a relapse occurs and the patient dies in nine months, then this treatment compares unfavourably with treatment B which is quite ineffective on patient 2 who has skin secondaries, but who lingers on for fifteen months.

If survival times were the only criteria, then treatment B, which was without effect, would be rated "better" than treatment A which at least had a temporary effect, and this would obscure the purpose of the trial which was to investigate the effect of the treatment on the cancer cell.

It is true that, if sufficiently large populations were contrasted, then these difficulties would be ironed out as there would be approximately the same number of skin and brain secondaries in each group. However, this is not practicable, so we have to be content with a possible maldistribution of such "deviants" as I have called them (Atkins, 1959) and see if there is not another criterion which we could use which obviates this difficulty.

The Mean Clinical Value, which Mr. Murray Falconer used to contrast the populations, is at once a more delicate and, in this context, a more appropriate index of response. In this method each lesion is examined at four-weekly intervals after treatment and a mark is given to it depending upon whether it has improved (2 marks), worsened (0 marks), or there is some doubt (1 mark). The marks are then added together and divided by the number of lesions to obtain an average, and this figure is multiplied by six, simply to bring it to a less unwieldy number. The effect, as we have seen, is to grade each patient at her four-weekly follow up with some mark between 12, which would indicate that all the lesions were getting better, and 0, which would indicate that all the lesions were getting worse. Some criticisms have been levelled at the method because it is asserted that it tries to be too exact, but assessment requires no more refined judgment than to say if a lesion is better or worse or that it is impossible to decide. Intermediate marks between 0 and 6, or between 6 and 12 occur because not all lesions respond to treatment to the same extent or at the same time. We have now used the M.C.V. method for many years at the Guy's Hospital Breast Clinic and we find it a most useful tool in the investigation of the response of these patients. It obviates the difficulty encountered in using the survival times as criteria in that, whatever the survival time, if the lesion responds the case will be given a high mark and if it fails to respond a low mark, irrespective of where the lesion is. Since therefore the principal aim is to find out the effect of treatment on the behaviour of the cancer cell, we regard this as the more important, as well as being the more delicate, index.

Mr. Murray Falconer has shown, using the M.C.V. as a standard, that the response to hypophysectomy is better than the response to adrenalectomy with oophorectomy. As befits a more elegant method, this difference is significant at the 0·03 level. By "better", therefore, we mean that patients survive longer after hypophysectomy than they do after adrenalectomy and that during the period of survival there is a more effective reduction in the volume of cancer tissue.

This, however, is not necessarily the whole story. We are dealing with what may be called heterogeneous populations. Apart, that is, from the natural heterogeneity of any sample population in respect of age, build, blood pressure and so on, there is a heterogeneity in regard to the type of lesions which are being investigated. All we have purported to show within the conventional limits of statistical acceptability is that when one such heterogeneous population is compared with another such heterogeneous population chosen by randomization, that population treated by hypophysectomy responds better than the population treated by adrenalectomy. Although the distribution of lesions and age groups in these two heterogeneous populations is approximately the same, we can make no statement about whether our findings are true at all ages or with all manifestations.

The fact that the bulk of our population is over 50 might, when the whole population is considered, mask the beneficial effect of adrenalectomy in the younger age group. In order to determine these matters, a great deal more detailed investigations of much larger populations will be necessary and it is for this reason, amongst others mentioned below, that it would be quite improper at this stage to give up adrenalectomy in favour of hypophysectomy when so little is known about the details of the behaviour of both these methods.

How Much Better?

The fact that we have shown that hypophysectomy is better than adrenalectomy at the 0·03 level of statistical probability gives no indication of the degree of difference between these two measures. It does not imply that the difference is decisive, meaningful or worth while or indeed—in the colloquial sense of the term—significant! The term "significant", like the terms "confidence" and "fiducial limits", has been appropriated by the statisticians to define a mathematical parameter very much more restricted in its implications than its colloquial use would allow. This is a pity, because it has led to considerable misunderstanding on the part of those who have not had a statistical training and who are inclined to believe that if the difference between two populations is statistically very significant, that this difference must be very considerable, meaningful, worth while or what I have called "determinant", implying that it determines policy, and indeed what *they* would call "significant".

How much better is hypophysectomy than adrenalectomy, and is the difference determinant? The average survival for hypophysectomy is 10·8 months and for adrenalectomy 9·0 months. During this period of survival the average M.C.V. for hypophysectomy is 6·57 and for adrenalectomy 5·48. Furthermore there is a wide variation of individual figures about all four of these means.

If such considerations can be given mathematical precision, and I doubt this, these figures 10·8 : 9·0 and 6·57 : 5·48 do indicate roughly the order of the degree of difference between these two procedures. It is the sort of difference which, if the better method carried any specific disadvantages, would be immediately wiped out by practical considerations. In fact, of course, the two procedures are, from the patient's point of view, somewhat nicely balanced. Hypophysectomy has the advantage that it is a one-stage procedure (whereas bilateral adrenalectomy with oophorectomy is usually carried out in two stages) but it has the slight disadvantage that the sense of smell may be impaired, and there is a somewhat higher incidence of "cushingoid" features, which, however, can be controlled by giving thyroid extract. The mortalities of the operations, that is cases dying within twenty days of operation, have in our series been 7/79 for adrenalectomy, and 3/70 for hypophysectomy, the standard deviations being 12 and 10·8 respectively.

Hypophysectomy, however, is an operation which can be carried out safely by only a very few surgeons. Certainly it would be quite improper to read into our findings a recommendation that adrenalectomy should be discarded for hypophysectomy in the treatment of advanced cancer of the breast.

About 8,000 women die of cancer of the breast each year in England and Wales. Of these about 7,000 would be suitable for treatment by hypophysectomy at some stage in their illness, although this figure could be materially reduced by a method of preselection shortly to be published. Even if the number of adequately trained surgeons were doubled or preselection halved the number of suitable cases, the numbers would be unmanageably large. It may be urged that not quite such skill is demanded for stalk section or yttrium 90 implantation, though I would doubt this in regard to the latter, so that if these methods were allowed, there would be a sufficient number of qualified surgeons to deal with advanced breast cancer by destruction of the pituitary gland. We have, however, no evidence that stalk section or yttrium implantation is as good as surgical hypophysectomy or even adrenalectomy with oophorectomy, so that no statement can be made about this matter.

For a few years, therefore, no doubt, adrenalectomy will retain its place as a satisfactory and safe method of treatment for advanced cancer of the breast in the hands of any reasonably competent general surgeon. It is well that this should be so and, furthermore, that the most ethical way of choosing which patient should be subjected to which operation is still by randomization. Originally this method was ethical because we did not know which was the better procedure; it is now the most fair because not every patient can undergo what has been shown to be the slightly better procedure.

In this way it will be possible to continue our studies into the more detailed aspects of the effect of these operations. The series can be broken down according to age, type of manifestation and so on, so that additional evidence will be forthcoming on these points of detail.

Finally, if we have shown a significant difference in the effect of these two methods of treatment, but that the degree of difference is not such as to make it worth while to condemn one method in

favour of the other, has this finding any value? Certainly from the scientific point of view this is the case. We have shown that hypophysectomy achieves something that cannot be achieved by adrenalectomy and this is an important scientific fact. It will direct the attention of research workers in this field to the growth hormone and other hormones specific to the pituitary, and to the effect of adrenal tissue lying outside the confines of the adrenal gland. In this way research into the endocrine effects on hormone-dependent growths will be more distinctly focused and the image more brightly illuminated.

REFERENCE

ATKINS, H. J. B. (1959) *Guy's Hosp. Rep.*, **108**, 423.

Interstitial Irradiation of the Pituitary

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THE development of the technique of transnasal implantation of the pituitary at the Royal Marsden Hospital is entirely due to the efforts of Mr. Peter Greening who performed the first implant more than five years ago (Greening, 1956). I have been associated with him in this work since 1956.

The history of interstitial irradiation of the pituitary goes back thirty years or so. Cushing implanted radon seeds via a craniotomy, into patients with basophil adenoma, and there have been several reports since of the use of radon in this way for the treatment of pituitary tumours. In 1936 Lodge described an approach via the orbit and ethmoid sinus to the sella turcica in cases where the latter had become grossly expanded by a tumour. He removed as much of the growth as possible and then implanted radon seeds. This same route is used by Bauer (1956) to insert a cannula into the gland.

The demonstration by Luft and Olivecrona (1953) of the value of surgical hypophysectomy in patients with metastatic breast cancer led inevitably to the search for a simpler method of destroying the normal gland.

External irradiation with conventional X-rays produces little or no effect upon this extremely radioresistant structure (Kelly *et al.*, 1958). The effect of a high energy proton beam is being studied (Tobias *et al.*, 1958). Electrocoagulation (Bauer, 1956) has not proved satisfactory because the electrode becomes covered with an insulating layer of charred tissue and further destruction is thus prevented. The injection into the gland of solutions of corrosives or of radioactive materials is dangerous because of the impossibility of limiting the fluid to the confines of the sella; it always leaks out and may damage surrounding structures.

Radon seeds were an obvious choice but experience showed that their penetrating gamma rays caused serious damage to the optic nerve which led to total blindness in many cases (Forrest *et al.*, 1956; Westminster Hospital, 1956).

Radioactive gold grains (^{198}Au) were first inserted via a transnasal cannula by Greening in February 1955, and at the same time, Forrest started using a similar technique for the insertion of radon seeds.

In 1953 Rasmussen *et al.* suggested, from experimental evidence, that yttrium 90, a pure beta ray emitter, would be a suitable source for producing localized destruction of the pituitary without damage to surrounding structures. Their experimental findings were confirmed by Yuhl *et al.* (1955) who introduced yttrium pellets at craniotomy. Yttrium was first used at the Royal Marsden Hospital in July 1956. ^{198}Au emits mainly gamma rays which are less penetrating than those from radon. A small quantity of beta rays is also produced but these travel a very short distance. The half-life of the two isotopes is, for all practical purposes, the same. Isodose curves (Fig. 1) show the much more rapid fall off with distance of the radiation from yttrium compared with that from gold.

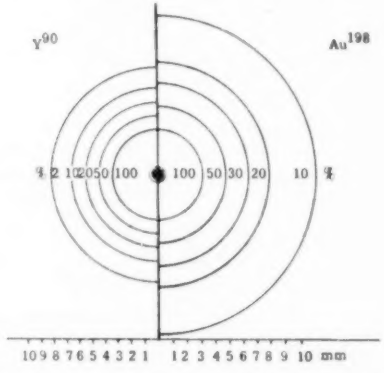

FIG. 1.—Isodose curves for ^{90}Y and ^{198}Au. (Doses equated at 3 mm from source.) Modified from Scheer *et al.* (1959) by kind permission.

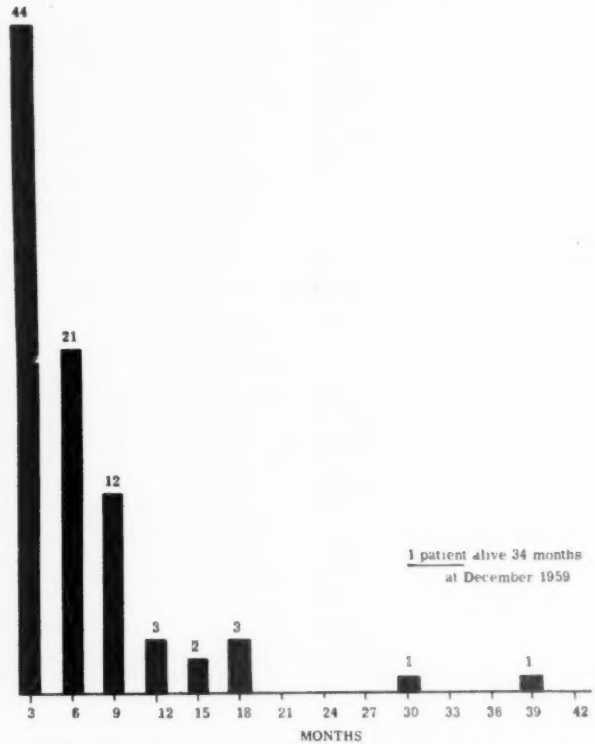

FIG. 2.—Survival after implant (non-responders) = 88 patients.

From February 1955 to March 1958, 100 patients with metastatic carcinoma of the breast were treated by implantation of the pituitary. Gold was used in 54 cases and yttrium in 36. The remaining 10 patients had first one and later the other isotope implanted. Screened gold grains, 2·5 mm long, 0·8 mm in diameter and with a sheath of platinum 0·15 mm thick were used at first, but later we changed to unscreened rods 5·0 mm long and 0·8 mm in diameter.

The operation is carried out under antibiotic cover, and cortisone 50 mg daily is started on the day before operation for those patients not already receiving it. It was withheld from some of the early cases and the onset of signs of adrenal insufficiency (usually within the first week after operation) was taken as an indication that the pituitary had been destroyed. This practice has been abandoned because it imposes unnecessary discomfort and risk to the patient.

Results

2 patients only are alive. 12 (11 ^{198}Au, 1 ^{90}Y), had objective evidence of regression and one of these survives forty-four months after implant. The remainder lived for periods ranging from seven to forty months with an average survival of 19·4 months. The length of survival of the 88 non-responders is shown in Fig. 2. 65 were dead in six months, and 13 lived for less than one month. The few who lived for a long time serve only to remind us how chronic this disease can be.

These patients were specially selected for the trial of a new method of treatment and most of them had very advanced disease which all other forms of treatment had failed to control. In 5 only was pituitary implant done as the first planned treatment. 37 had had previous endocrine surgery, either oophorectomy alone or combined with adrenalectomy. None of them showed improvement after pituitary implant no matter what their response to the previous operation had been. This is not surprising in those cases treated by adrenalectomy, as response to pituitary ablation is rare after this operation. There was only one patient who relapsed after successful oophorectomy, and pituitary implant failed to induce further regression. It is obvious that no fair comparison can be made of the

results in this series with those obtained by other methods of treatment.

The extent of destruction of the pituitary was estimated in 39 specimens obtained at post-mortem and examined histologically. In 4, the gland was totally destroyed, 3 by ^{90}Y (11·9, 12·8 and 8·6 mc) and one by ^{198}Au (80 mc). In a further 7 cases the extent of destruction was estimated to be between 90% and 95% and the activity of the rods ranged from 34 to 115 mc of gold and from 5·4 to 11·7 mc of yttrium. The smallest amount of ^{90}Y known to have destroyed the pituitary was 8·6 mc and the largest amount that was proved not to have destroyed all the gland was 11·7 mc. Thus about 10 mc of ^{90}Y should be sufficient to produce total necrosis in most cases. In common with other workers, we have found that gold is not efficient in producing total necrosis and in one case 125 mc still left between 10% and 20% of apparently viable cells.

We were able, in a few patients, to correlate the clinical response with the extent of necrosis found at autopsy and the pre- and post-implant urinary gonadotrophin levels. This was so in 2 of the 12 cases showing objective regression. The extent of destruction was 100% in one and 95% in the other and the gonadotrophin levels fell to zero in both. Among the non-responders there were 8 patients in whom this combination of circumstances occurred. In 6, the extent of destruction was between 80% and 100%, and in all these the gonadotrophin excretion fell to very low levels after implant. In the other 2 cases the amount of pituitary destroyed was small, 10% in one and 33% in the other, yet there was a similar dramatic fall in the amount of gonadotrophin excreted. We must therefore accept with caution a fall in urinary gonadotrophin excretion as evidence of complete histological destruction of the pituitary although it probably reflects loss of function.

Complications

All patients develop a headache but this is not usually severe and is easily controlled by simple analgesics. Diabetes insipidus occurred quite often in the early post-operative period but lasted only a short time in most cases. A few patients required injections of vasopressin tannate. Bleeding was common but was not often severe although 2 patients required transfusion. Optic atrophy occurred in 3 patients and must be assumed to be due to the implant; unfortunately we did not have the opportunity of confirming at post-mortem that the blindness was in fact the result of radiation damage to the optic nerve. Although this is the most probable explanation, there was one patient whose blindness was discovered at autopsy to be due to a metastasis.

The most disastrous complication was meningitis which caused 10 deaths. C.S.F. rhinorrhœa and meningitis, either separately or together, occurred in 21 patients. The material implanted was gold in 9 and yttrium in 12. 10 patients developed rhinorrhœa which sooner or later ceased spontaneously. 5 patients developed rhinorrhœa and subsequently meningitis and all died. 6 patients developed meningitis without previous rhinorrhœa and 5 of these died. A striking feature of this complication was the variation in the elapse of time after implant before meningitis occurred. The diagram (Fig. 3) illustrating this point includes 2 patients suffering from diseases other than carcinoma of the breast. Antibiotic cover as long as the leak persisted was the only treatment employed. We have no experience of operations to cure this condition although we have experimented recently with the insertion of a plug of wax to close the hole in the floor of the sella as the cannula is withdrawn. Meningitis was extremely resistant to treatment and the clinical course varied from acute fulminating to chronic. At post-mortem multiple adhesions with much fibrinous exudate were commonly found and it is not surprising that antibiotics have little effect in such cases. The cause of the C.S.F. leak provides scope for speculation and it seems that there are several possibilities. There was no correlation between the activity of the rods and the development of rhinorrhœa, but there is no doubt that it occurs if rods are placed high up anteriorly; in this position they lie just under the diaphragma sellæ and may cause it to necrose (Forrest *et al.*,

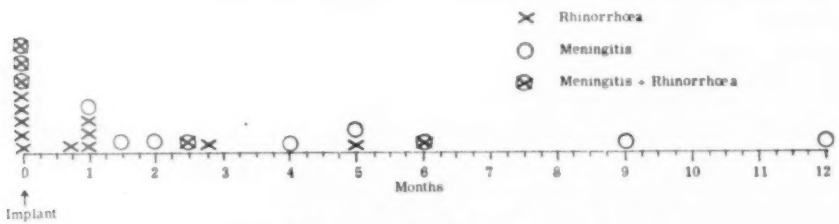

FIG. 3.—Onset of rhinorrhœa and meningitis following implant.

1959). Rhinorrhœa can, however, occur with properly placed rods and Forrest suggests that it is then due to overdosage, but this does not explain the immediate leak of C.S.F. which we have noted on several occasions on the introduction of the cannula low down near the floor of the fossa and we must seek another explanation. The cause, I believe, lies in abnormal anatomy and there are two variations from the normal which may be important. First, the depth of the fossa as shown radiologically does not necessarily indicate the depth of the gland which it contains. The pituitary may sometimes consist of no more than a flattened disc lying on the floor and in such a case the diaphragma is not stretched across the top but dips down to be closely applied to the upper surface of the gland. It is easy to see therefore, that a rod placed in the middle of the fossa and judged to be in the middle of the gland might in fact be lying above the diaphragma in the subarachnoid space. Secondly, the diaphragma sellæ is often deficient. Mahmoud (1958) found this to be so in 40 of 100 fossæ examined at autopsy. In some the deficiency is quite large and it is in such cases that I believe that the subarachnoid space may extend down into the fossa.

The high incidence of complications and the need to assess the results in the first 100 cases caused us to suspend the operation for a time. We have developed doubts about the superiority of yttrium over gold for the following reasons: (1) All but one of the 12 patients showing objective regression were implanted with gold. (2) The incidence of rhinorrhœa and meningitis was lower in the gold series (9 ^{198}Au, 12 ^{90}Y). We have also come to realize that the transnasal approach is not ideal. The only safe place to implant rods is low down near the floor of the fossa and the logical approach is a horizontal one. A horizontal approach via the nose is impossible in many cases and septal deviation and enlarged turbinates add to the difficulties of the operation. On the other hand, the transethmoidal route, which has been used by Bauer for twelve years, permits a horizontal approach to the fossa to be made in all cases and anatomical variations do not deflect the cannula. It also appears, theoretically at least, to be a more sterile route.

Finally, it is doubtful whether complete histological destruction of the pituitary is necessary to induce a remission. Bauer admits that he does not destroy the gland completely, in fact his patients do not need cortisone, and yet he obtains satisfactory results. These then are some of the problems yet to be solved before pituitary implantation can be established as a routine procedure.

REFERENCES

BAUER, K. H. (1956) *Arch. klin. Chir.*, **284,** 438.

——, and SCHWEITZER, L. A. (1958) In: Endocrine Aspects of Breast Cancer. Ed. A. R. Currie. Edinburgh: p. 56.

FORREST, A. P. M., BLAIR, D. W., PEEBLES BROWN, D. A., STEWART, H. J., SNADISON, A. T., HARRINGTON, R. W., VALENTINE, J. M., and CARTER, P. T. (1959) *Brit. J. Surg.*, **47,** 61.

——, BROWN, P. A., MORRIS, S. R., and ILLINGWORTH, G. P. W. (1956) *Lancet*, i, 399.

GREENING, W. P. (1956) *Lancet*, i, 728.

KELLY, W. A., EVANS, J. P., HARPER, P. V., and HUMPHREYS, E. M. (1958) *Surg. Gynec. Obstet.*, **106,** 600.

LODGE, W. O. (1936) *Brit. med. J.*, ii, 1257.

LUFT, R., and OLIVECRONA, H. (1953) *J. Neurosurg.*, **10,** 301.

MAHMOUD, M. E. S. (1958) *Brit. J. Radiol.*, Suppl. 8.

RASMUSSEN, T., HARPER, P. V., and KENNEDY, T. (1953) *Amer. Coll. Surg., surg. Forum*, **4,** 681.

SCHEER, K. E., GUDDEN, F., and BEKERUS, M. (1959) *Nuclear Med.*, **1,** 91.

TOBIAS, C. A., LAWRENCE, J. H., BORN, J. L., MCKOMBS, R. K., ROBERTS, J. E., ANGER, H. O., LOW-BEER, B. V. A., and HUGGINS, C. B. (1958) *Cancer Res.*, **18,** 121.

Westminster Hospital (1956) *Rep. Brit. Emp. Cancer Campgn.*, **34,** 173.

YUHL, E. T., HARPER, P. V., RASMUSSEN, T. B., and BERGENSTAL, D. M. (1955) *Amer. Coll. Surg., surg. Forum*, **6,** 489.

Localization of Radio-active Implants with Image Intensification and Television

By J. J. STEVENSON, M.D., D.M.R.

The Royal Marsden Hospital and The Institute of Urology

DURING the past five years we have carried out implantation of the pituitary gland with radio-active material in more than 200 patients.

At the beginning it was felt that the localization of the introducing needle and subsequent implant could be most conveniently done by means of fluoroscopy in two planes. However, it proved impossible to perceive adequate detail on the conventional fluorescent screen and moreover the use of very subdued room lighting with intermittent total darkness gravely handicapped the surgeons and anæsthetists concerned. For some time previously we had been making use of the image intensifier in the examination of the gastro-intestinal and urinary tracts at the Royal Marsden and St. Paul's Hospitals. This is an electron optical tube consisting essentially of two fluorescent screens with a high potential difference between them. When X-rays strike the front screen it fluoresces in the normal manner.

Electrons are emitted from its posterior surface in direct proportion to the amount of fluorescence immediately in front. These being negatively charged particles are accelerated across to the anode end of the tube and are focused on the smaller screen at the rear. Owing to the difference in the areas of the two screens and the impact with which the electrons strike the smaller, its brightness is several hundred times greater than that of the other, and similarly to that of any conventional fluoroscopic screen. With the aid of a simple optical attachment it is possible for the observer to use smaller amounts of X-rays and at the same time see much more detail. Furthermore, as examinations could be carried out in fully lighted rooms the instrument was particularly suitable for certain minor operative procedures in the X-ray department such as hysterosalpingography and ascending pyelography. It was so successful on the first occasion on which it was used for the lateral screening of the gold grain implants which we were then using that in a few weeks an apparatus was constructed which permitted screening in two planes using the same image intensifier and X-ray tube. An old floor-ceiling tube stand was used with a specially made arm which was pivoted about its centre. The intensifier was fixed at one end and the X-ray tube at the other. Once it had been adjusted it was found possible to change the plane of screening in three or four seconds. The operator was able to work unimpeded by the equipment, the radiologist was able to see clearly and the dose of scattered radiation was very low indeed. Subsequently, commercial models of the biplane fluoroscope were made by European companies. These machines are more versatile and are particularly suitable for orthopædic operations.

Perhaps the greatest drawback of the intensifier was the difficulty which surgeons had in adapting themselves to the use of the rather awkward viewing attachment. This also applied to our usually large audience, each of whom nevertheless demanded "a look" and thus added considerably to the operating time. Towards the end of last year we felt that these problems could be solved by the use of an industrial television chain in conjunction with the image intensifier. This equipment is comparatively simple and inexpensive and can be operated with only a little training. The camera is smaller and lighter than the reflecting viewer which it replaces. Owing to the short distance between the output phosphor of the intensifier and the photoconductive layer of the Staticon tube of the camera an optical link consisting of two 1 in. f 0·95 lenses is used. A very convenient mobile console cabinet was constructed in Professor Mayneord's physics workshop which houses the 8½ in. monitor, the camera control unit and the panel (Fig. 1). Detail on the television screen in the frontal and sagittal planes is adequate, but is not quite as good as with the optical device. The current in the X-ray tube has to be approximately doubled. However, there should be no increase in dose to the observers as the monitor can be placed some distance away from the patient. We have found no major disadvantages in its use and the operating time has been speeded up considerably.

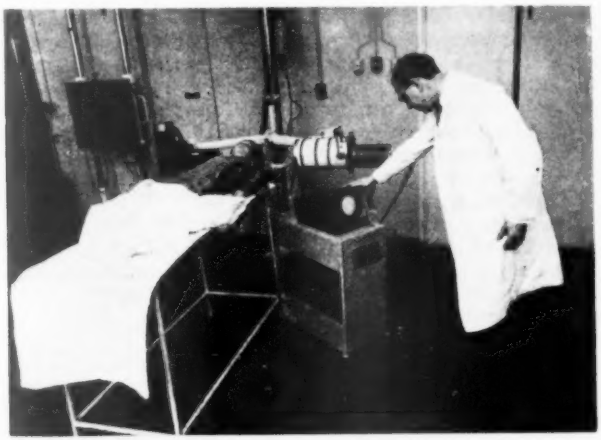

FIG. 1.—Biplane fluoroscope fitted with industrial television chain.

Meeting
April 8, 1960

Some Observations on Neuromuscular Disorders of the Œsophagus

[*Summary*]

PRESIDENT'S ADDRESS

By Professor A. S. JOHNSTONE, F.R.C.S.Ed.
Leeds

NEUROMUSCULAR disorders of the œsophagus can be divided into two main groups. By far the commonest lesion is cardiospasm with its characteristic changes of narrowing in the terminal œsophagus with dilatation above, irregular contractions and slight thickening of the wall. On the other hand there is a small, clearly defined, group of patients who are found to have gross muscle hypertrophy of the lower half of the wall in association with abnormal contractions in this segment, excluding the termina! 2 to 3 cm where no abnormal changes are found. Symptomatology, age group and sex incidence are quite different from those in cardiospasm. Four cases confirmed at operation were described and an additional 39 cases of abnormal contractions which do not fit into either group were analysed. It was felt that this collection of abnormalities, many of which would be termed corkscrew œsophagus, pseudo-diverticula, &c., have many features in common with the diffuse hypertrophy group and they must be regarded as being of the same ætiology. Sloper's review of the ætiological factors was discussed and stress was laid on a neuromuscular disorder probably associated with vagal over-activity. There was evidence to show a strong relationship between diffuse hypertrophy and diseases of the upper alimentary tract; it was also considered that in some patients it might have a psychosomatic origin. Some evidence was produced to show that abnormal contractions could be related to small peptic ulcers in the lower œsophagus, generally associated with hiatus hernia. Reference was made to Torrance's work on vagal stimulation as a cause of hiatus hernia.

BIBLIOGRAPHY

BROMBART, M. (1956) La Radiologie Clinique de l'Œsophage. Paris.
JOHNSTONE, A. S. (1956) *Proc. R. Soc. Med.*, **49**, 539.
—— (1958) In: A Textbook of X-ray Diagnosis. Eds., S. C. Shanks and P. Kerley. London: **3**, 53.
SLOPER, J. C. (1954) *Thorax*, **9**, 136.
TEMPLETON, F. E. (1944) X-ray Examination of the Stomach. Chicago.
TORRANCE, H. B. (1958) *J. Roy. Coll. Surgeons, Edin.*, **4**, 54.

Section of Proctology

President—ALAN H. HUNT, M.Ch.

Meeting
January 13, 1960

A Comparative Trial of Salazopyrin,[1] Prednisone and Hydrocortisone Retention Enemata in the Out-Patient Treatment of Left-sided Colitis

Preliminary Report

By J. E. LENNARD-JONES, M.B., M.R.C.P.,[2] A. J. LONGMORE, M.D., F.R.C.P.(C)., and F. AVERY JONES, M.D., F.R.C.P.

London

ENTHUSIASTIC reports have come from Sweden (Svartz, 1956) and America about the efficacy of Salazopyrin in the treatment of ulcerative colitis. Moertel and Bargen (1959) concluded that this drug benefited two-thirds of the patients to whom it was given and in one-third full remission was achieved; an improvement, they claim, comparable with the best results from corticosteroids. Cortisone is known to be an effective drug in the treatment of colitis (Truelove and Witts, 1955); Newell and Avery Jones (1958) reported that prednisone brought about remission in 2 out of 3 cases of active proctitis. Truelove (1958*a*) described similarly successful results using retention enemata of hydrocortisone hemisuccinate in mild or moderately severe cases of colitis. Both oral prednisone and hydrocortisone enemata have been shown by these authors to be much more effective than inert substances given as a control.

About one-third of the patients who improve initially relapse within the next few months, whichever treatment is given. Local hydrocortisone alone seems to be free of any undesirable side-effects; the potential dangers of oral corticosteroid therapy are well known. Salazopyrin also gives rise to unpleasant side-effects fairly often, including occasionally reversible hæmolytic anæmia (Spriggs *et al.*, 1958) and agranulocytosis (Moertel and Bargen, 1959).

The Present Trial

We have investigated by a direct comparative trial the relative effectiveness of these three remedies as out-patient treatment for left-sided colitis. Since controlled trials using a placebo have proved that two out of the three treatments are effective, we did not consider it necessary to treat a group of patients with an inert substance in this series. The criteria for including a patient in the trial were: (1) Each must be suffering from an exacerbation of left-sided colitis, proctosigmoiditis, or proctitis. (2) There must be no contraindication to the use of any of the three treatments.

After a patient had been deemed suitable for the trial, one of the three treatments was allocated according to a random scheme.

Salazopyrin was given in a dose of 4 g daily and the patient was instructed to reduce the dose if severe side-effects occurred. Prednisone, 60 mg daily, was given for the first week, 45 mg daily for the second week and 30 mg daily for the third week. The patients given hydrocortisone enemata made up a fresh solution each night of 100 mg of hydrocortisone (as hemisuccinate sodium) in 150 ml of normal saline and infused it into the rectum on going to bed, using a modified blood transfusion set (Truelove). Each patient who received this treatment was carefully instructed in the self-administration of the enema.

After treatment for three weeks patients were seen again and any change in symptoms or at sigmoidoscopy was noted. The sigmoidoscopic appearance was graded as follows:

Active disease: œdematous, friable mucosa.
Healing phase: drier, granular mucosa, only slightly friable.
Inactive disease: dry, granular mucosa, not friable, with or without vascular pattern.

When no apparent benefit resulted from the treatment in three weeks, it was considered a "failure" and the trial ended. A treatment beneficial during the first three weeks was continued in reduced dosage until full remission or maximum benefit was achieved, and then stopped. The results in these patients were assessed at three and six months after starting treatment and classed:

Success: remission began soon after starting treatment and maintained since.
Partial success: symptoms partially controlled or early improvement followed by a relapse.

[1]Salicylazosulphapyridine. [2]Member, Scientific Staff, Medical Research Council.

TABLE I.—COMPARABILITY OF THE THREE TREATMENT GROUPS

	No. of patients	Mean age	Males	Number in relapse	Symptoms		
					Diarrhœa, blood and mucus	No diarrhœa; blood and mucus	Diarrhœa only
Salazopyrin	20	38 (S.D. 16)	7	10	11	8	1
Prednisone	20	44 (S.D. 14)	8	12	13	7	0
Local hydrocortisone	20	45 (S.D. 17)	12	15	13	7	0

TABLE II.—PRELIMINARY RESULTS AT THREE AND SIX MONTHS

	3 months				6 months			
	Success	Partial success	Failure	Total	Success	Partial success	Failure	Total
Salazopyrin	8	5	5	18	6	4	5	15
Prednisone	6	5	4	15	5	5	4	14
Local hydrocortisone	2	3	12	17	1	1	11	13

The Patients in this Series (Table I)

60 consecutive patients who attended the Out-Patient Department at St. Mark's Hospital fulfilled the criteria described and have been admitted to the trial. They were divided into groups of 20 patients, each treated with one of the three remedies. Patients have been included in the trial once only. All were living normal lives and experienced little or no constitutional upset from their disease. We did not consider it justifiable to perform a new barium enema specially to define the extent of the disease at the time of the trial. Those patients who were seen for the first time had a barium enema when admitted to the trial; others had previously had a barium enema showing left-sided colitis.

Most complained of diarrhœa with the passage of blood and mucus, some had normal or constipated bowel actions but with blood and mucus, and one had diarrhœa only. Patients with these different symptoms were distributed evenly between the three groups (Table I).

The difference in age and sex distribution between the groups was small. In the hydrocortisone group more patients were treated for a relapse rather than for the first attack, than in the other two groups.

Results

At the moment we can only report preliminary results because the trial is still in progress and in some patients the data at three or six months are incomplete.

After three weeks' treatment the greatest proportion of patients free of symptoms was in the prednisone group and the lowest in the local hydrocortisone group (Fig. 1). The difference between these groups is such as would have occurred by chance only once in fifty times. 7 out of the 15 patients who told us that they

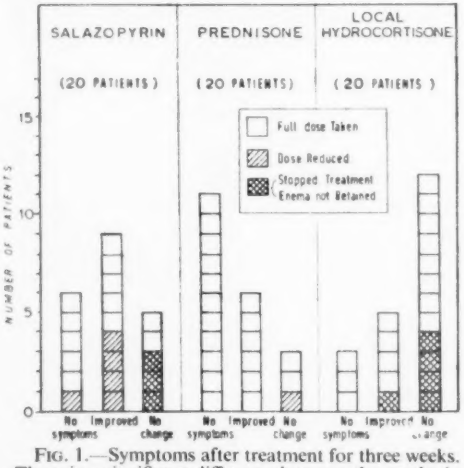

FIG. 1.—Symptoms after treatment for three weeks. There is a significant difference between the results in the prednisone and local hydrocortisone groups ($\chi^2_c = 7{\cdot}8$, n = 2, P = 0·02).

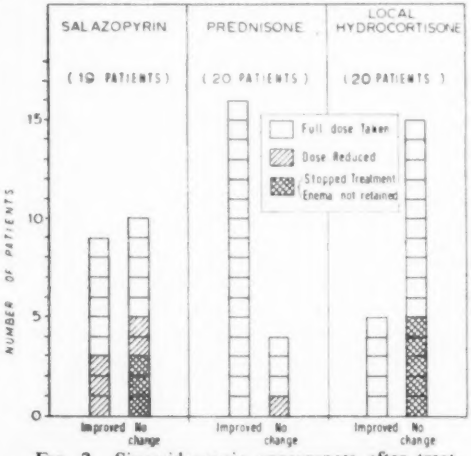

FIG. 2.—Sigmoidoscopic appearances after treatment for three weeks. There is a significant difference between the results in the prednisone and local hydrocortisone groups ($\chi^2_c = 10{\cdot}0$, n = 1, P = <0·01).

retained the hydrocortisone solution in the rectum more than two hours improved during the treatment. Objective assessment by sigmoidoscopy bears out the symptomatic changes (Fig. 2). Again, the best results followed prednisone and the worst local hydrocortisone; the difference between them would only have occurred by chance once in 100 times.

At three and six months our results so far show approximately equal results in the Salazopyrin and prednisone groups (Table II). This is because some of the patients, symptom free after three weeks' treatment with prednisone, have now relapsed. The relapse sometimes occurred as the dose of the drug was reduced and sometimes soon after stopping the treatment.

There is no doubt that most patients prefer prednisone to Salazopyrin. 6 of our patients given prednisone experienced mild side-effects and 1 reduced the dose on account of syncopal attacks. 1 patient complained of colic after the retention enemata. With Salazopyrin over half our patients complained of side-effects, usually anorexia, nausea or malaise. 3 patients (accounting for 3 out of the 5 failures) could not take the drug even in small doses, 5 others could take only a reduced amount (Fig. 1). Side-effects were more frequent among these patients than in most reported series, possibly due to the fact that our patients were feeling well and were thus conscious of mild malaise or digestive upsets. One on Salazopyrin developed a skin rash; we have not observed any hæmatological complications.

Discussion

The results presented support the contention that Salazopyrin is an effective remedy in ulcerative colitis. The response is slower than that to prednisone but at three and six months after starting treatment there is little to choose between them. Prednisone is the most effective for the immediate relief of symptoms but the relapse rate is high and corticosteroids are potentially dangerous. Salazopyrin frequently gives rise to unpleasant side-effects but dangerous complications are rare.

The elegant controlled trials of Truelove (1958*b*) and Watkinson (1958) have proved conclusively that local hydrocortisone enemata can be an effective remedy in the type of case we have treated. We do not think that our disappointing results can be attributed to the number treated in relapse, because the treatment failed in 4 out of 5 patients treated during a first attack (4 of whom retained the solution in the rectum all night). Neither can the failure be attributed to the extent of the disease, because in half the cases given this treatment a barium enema was normal or showed only minimal changes at the time of the treatment, and in 3 an upper limit to the disease could be seen on sigmoidoscopy. We think it most likely that the treatment often failed because a rather complex and inconvenient mode of administration was used under ordinary out-patient conditions. Our "failures" include 1 patient who did not give himself the treatment because of emotional aversion to it and 3 patients who completely failed to retain the enemata. Nearly half the patients who told us that they were able to retain the solution in the rectum for longer than two hours improved during the treatment.

Both Truelove and Watkinson took great care in demonstrating the technique of self-administration of the enemata to their patients; the latter admitted his patients to hospital for two to three days for this purpose. Our results suggest that out-patient explanation is not enough and that a practical demonstration, possibly in hospital, is needed for success. We think that retention enema treatment using a more convenient technique and a more stable drug, such as prednisolone 21-phosphate, is likely to give good results under out-patient conditions.

We suggest the following *out-patient regime for patients with left-sided colitis*. We emphasize that we are not including ill patients in hospital but only patients having little constitutional upset and living normal lives.

A. *Disease Extending Above the Rectum*

(1) Begin with *Salazopyrin* (convenient, moderately effective and safe).

(2) If this fails, use *local treatment* (retention enemata of hydrocortisone hemisuccinate or prednisolone 21-phosphate).

(3) If other treatments fail or a prompt response is specially needed use *prednisone* (the most effective drug of the three for rapid relief but potentially the most dangerous).

B. *Disease Confined to the Rectum*

Begin with suppositories of prednisolone 21-phosphate (Truelove, 1959; Lennard-Jones *et al.*, unpublished data).

Acknowledgment.—We wish to thank Glaxo Laboratories for supplying the hydrocortisone hemisuccinate sodium used in this trial.

REFERENCES

MOERTEL, C. G., and BARGEN, J. A. (1959) *Ann. intern. Med.*, **51**, 879.
NEWELL, A. C., and JONES, F. A. (1958) *Proc. R. Soc. Med.*, **51**, 431.
SPRIGGS, A. I., SMITH, R. S., GRIFFITH, H., and TRUELOVE, S. C. (1958) *Lancet*, i, 1039.
SVARTZ, N. (1956) *Gastroenterologia, Basel*, **86**, 683.
TRUELOVE, S. C. (1958*a*) *Proc. R. Soc. Med.*, **51**, 429.
—— (1958*b*) *Brit. med. J.*, ii, 1072.
—— (1959) *Brit. med. J.*, i, 955.
——, and WITTS, L. J. (1955) *Brit. med. J.*, ii, 1041.
WATKINSON, G. (1958) *Brit. med. J.*, ii, 1077.

DISCUSSION

Dr. S. G. Flavell Matts (Bristol): I was interested that Dr. Lennard-Jones found the method of slow intrarectal infusion of hydrocortisone cumbersome and time consuming, and not very portable. It can also be difficult and time consuming to explain to the patient the method of setting up and administering it. In our experience of this therapy we have had satisfactory results, but have noted the drawbacks.

In view of these I have been trying to develop a simpler administration of intrarectal therapeutic solutions. A trial has just been completed of an alternative method of local therapy for ulcerative colitis.

This consists of a solution of a soluble prednisolone (prednisolone 21-phosphate) given in the form of a small retention enema, from a disposable plastic bag.

The patient gives this to himself every night on retiring to bed, the time taken being about five minutes. The solution is usually retained all night, and so far no technical difficulties have been encountered.

It is a method which particularly lends itself to out-patient work as the bags are portable and easy to dispense. The method of use can be explained to the patient in a few seconds.

The trial has been conducted in two parts: (1) A double blind trial employing sequential analysis to establish the value of the method. (2) Assessment on a larger number of patients. All had acute or relapsing ulcerative colitis, and were mainly out-patients. Admission to hospital was unnecessary in most cases.

The results were encouraging. Improvement was obtained in over 90%, sometimes rapidly and dramatically. If therapy is continued from four to eight weeks, a remission can usually be expected. The patients who responded best were those with fairly acute left-sided ulcerative colitis, but surprisingly good results have been obtained in the generalized disease.

The advantages of this method are numerous, particularly its simplicity, the time saved to patient and doctor and its ease for out-patient work; in suitable cases it may easily be combined with systemic therapy. The detailed results are published in the *Lancet*, together with an account of the technique (Matts, 1960).

REFERENCE

MATTS, S. G. F. (1960) *Lancet*, i, 517.

Irradiation Damage to the Bowel

By C. I. COOLING, F.R.C.S.

London

IRRADIATION damage to the bowel was the subject of a Hunterian Lecture in 1938 by Professor T. F. Todd of Manchester, but it does not appear to have been discussed at a meeting of this Section. Although it is a relatively uncommon lesion it can present the proctologist with a difficult problem.

The usual cause of irradiation damage to the bowel is treatment of carcinoma of the cervix by the conventional Stockholm radium method, but any external irradiation can act in a similar manner. Brick (1955) recorded damage to the stomach, small intestine and colon following supervoltage therapy to the abdomen. Bloom (1959) commented on the obvious advantages of supervoltage therapy for treating deep-seated tumours, but also spoke of the damage it can produce to other structures.

Conventionally, carcinoma of the cervix is treated by the insertion of a tube of radium into the uterus and packages of radium placed in the vaginal fornices. The dose is controlled by the time factor to give about 6,000 mg hours of irradiation, and may be followed by external irradiation to the parametria. If the radium slips or is in a bad position, an unexpected "high spot" of irradiation can occur to the rectum causing a localized area of overdosage.

All authors agree that there is a great deal of variation in the sensitivity of individual tissues to irradiation. Nevertheless, attempts to cure tumours by high dosage may achieve their object at the expense of damage to other structures.

At the Royal Marsden Hospital the insertion of the radium in these cases is checked by means of a scintillation probe dosimeter, which measures irradiation being received by the bladder and rectum. If a high dose of irradiation is given to the rectum the radium packages are readjusted. This control requires the support of a physics department; unfortunately few hospitals possess these facilities.

It is difficult to assess the incidence of rectal reactions, which must vary with techniques, stage of disease and age of the patient. Strickland (1954) recorded rectal damage in 2·4% of 501 cases treated in the years 1947 to 1952. Requarth and Roberts (1956) reported a similar incidence of 2·1% in the University of Illinois, but with a subsequent mortality of 33·3%; Wigby (1943) of Houston found that a colostomy was required in 7·9% of his cases.

Irradiation on the tissues produces initial œdema and congestion, with necrosis or hyaline degeneration. Endarteritis of the small vessels is a prominent feature, and necrosis, ulceration, fibrosis and stenosis of the bowel wall occur in varying degree, leading to fibrosis and stricture.

Todd (1938) classified the rectal reactions into

FIG. 1.—Barium enema showing long stricture in pelvic colon.

early and late. Early reactions are not our concern. They occur at the end of or during treatment, and are the reactions of any mucous membrane to irradiation. The symptoms are mild and subside in a few weeks. These cases belong to the group of so-called "factitial proctitis". If treatment is necessary rectal washouts, liquid paraffin and opiates soon relieve the diarrhœa and tenesmus.

The late reactions are more sinister and occur a few months or occasionally years after treatment. These Todd divided into intrinsic reactions or localized radionecrosis affecting only the bowel wall, and extrinsic reactions when indurated bowel lies in a pelvis full of fibrous tissue. In the American literature these lesions have been classified as Groups I–IV, from proctitis to advanced fibrosis with rectovaginal fistula.

The crux of the problem is the similarity to recurrent carcinoma in the pelvis. Such a patient, Mrs. A. N., aged 69, was treated with radium for carcinoma of the cervix. Four months later she developed rectal pain and bleeding due to an ulcer on the anterior rectal wall, 8 cm from the anal margin. There was concern that this might be malignant but biopsy was never positive. Under conservative treatment the ulcer healed in eighteen months, and she died four years later, tumour free.

In contrast, Mrs. S., aged 80, was treated by supervoltage therapy for carcinoma of the bladder. Two years later she had similar symptoms of rectal pain and bleeding. A rectal stricture was present but the bladder was clear of tumour. Nevertheless, the symptoms were due to a recurrence of tumour in the pelvis invading the rectum.

Rectal hæmorrhage can be severe with these late irradiation reactions and fatalities are not unknown. In Mrs. E. J., aged 52, rectal symptoms occurred ten months after completion of radium treatment. A barium enema showed a long stricture in the pelvic colon (Fig. 1) and it was impossible to say whether or not it harboured neoplasm. Laparotomy revealed a fibrous pelvic colon which was mobilized and resected leaving a temporary colostomy. She suffered persistent bleeding from the distal rectum and required blood transfusions. Eventually a massive hæmorrhage proved fatal, and at autopsy ulceration was found in the rectum. Usually a colostomy is sufficient to rest the bowel and control the hæmorrhage, but if it persists, as in this patient, a more radical surgical approach would seem desirable.

Another patient, Mrs. E. H., aged 37, developed a stricture in the rectosigmoid. Rectal bleeding and diarrhœa appeared seven months after radium treatment. The stricture was resected and its benign nature confirmed, that of excessive fibrosis throughout the bowel wall. She is alive and well, and free of tumour four years later. If a fibrous stricture occurs in the rectum, simple dilatation is all that is required.

The extreme type of extrinsic reaction with massive fibrosis is a difficult problem, the patient usually ending with a colostomy.

Mrs. E. F., aged 53, was treated by radium therapy in 1949. Two months later she developed rectal ulceration, fibrosis and a rectovaginal fistula. After four unsuccessful operations on the fistula, she was left with a colostomy. One of these operations had been an attempted closure with a lined perineal flap by a plastic surgeon.

In 1957 she attended the Gordon Hospital requesting to be rid of her colostomy. The fistula was present, the rectum stenosed and the pelvis solid with fibrous tissue. The rectal stricture responded to dilatation, but the fistula was large and low in the rectum. Seven months later a laparotomy was performed. A posterior pelvic evisceration was performed, digging out the uterus, vagina, rectum and fistula from this solid mass, leaving the pelvic colon and a 1-in. rectal stump. Intestinal continuity was restored, with the anastomosis in the perineum after eversion of the rectal stump. There was a partial breakdown of the suture line which subsequently healed, and the colostomy was closed a year later. She has normal bowel function and, fortunately, normal rectal control. There was no evidence of tumour in the specimen, but to obtain this cure she has gone through ten troublesome years.

With these problems, it is important to pursue the diagnosis and not abandon a case as a hopeless pelvic recurrence when in fact it is tumour

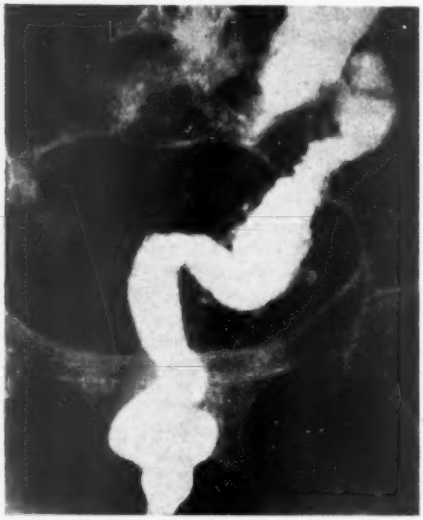

FIG. 2.—Barium enema to show associated rectal stricture and diverticulitis.

free, or to recommend further palliative irradiation to what is already a case of over-irradiation.

The following cases present a few points of further interest.

A woman, aged 70, developed a rectal stricture one year after radium treatment. At routine gynæcological follow-up she was noted to be tumour free and was reassured, but her rectal symptoms attributed to the radium slowly worsened. After *fifteen years* she was referred for a surgical opinion. Treatment with rectal washouts and paraffin emulsion brought rapid relief. A barium enema (Fig. 2) designed to produce a picture of a rectal stricture also demonstrated diverticulitis. Was the marked diverticulitis and not the rectal stricture responsible for most of her symptoms?

Another patient, aged 53, developed a metastasis in the left pubic bone from a carcinoma of the thyroid; she was treated by three courses of external irradiation. A full therapeutic dose of radioactive iodine was given later to ablate the residual thyroid tissue in the neck in the hope of persuading the metastasis to take up further doses of isotope. At this time she developed profuse rectal bleeding and the pelvic metastasis became tender. To bring the symptoms under control transfusions and a temporary colostomy were necessary.

The dose of irradiation received in the rectum from the isotope was extremely small, but the dose of external irradiation was sufficient to account for the rectal reaction. The administration of the isotope at that time was unfortunate, as it appeared responsible for the symptoms. Had the metastasis in the pelvis taken up the isotope this could have been the case.

Another aspect was encountered in a woman aged 31, who received external irradiation to enlarged lymph nodes in the left groin and two years later developed rectal symptoms. A barium enema revealed localized colitis or possible radiation damage of the pelvic colon. On sigmoidoscopy, the bowel was normal to 15 cm at which point there was an ulcer and a stricture which did not appear to be typical of ulcerative colitis. Her symptoms continued, and six years later she had progressed to a total colitis—allowing scope for speculation on the relationship.

Finally, we must remember the number of radiation-induced tumours now being reported in the literature in regions such as the pharynx and skin. I do not know of a reported case of such a tumour in the rectum, but with the increasing use of supervoltage therapy for pelvic tumours and greater tissue penetration, have we seen the end of this problem—or the beginning?

Acknowledgments.—I wish to thank the surgical staff of the Royal Marsden and Gordon Hospitals for permission to use the case records, and the photographic departments of the Westminster Hospital Medical School, Royal Marsden Hospital and Chester Beatty Institute for the illustrations.

REFERENCES

BLOOM, H. J. G. (1959) *Proc. R. Soc. Med.*, **52**, 495.
BRICK, I. B. (1955) *Arch. intern. Med.*, **96**, 26.
REQUARTH, W., and ROBERTS, S. (1956) *Arch. Surg., Chicago*, **73**, 682.
STRICKLAND, P. (1954) *Brit. J. Radiol.*, **27**, 630.
TODD, T. F. (1938) *Surg. Gynec. Obstet.*, **67**, 617.
WIGBY, P. E. (1943) *Amer. J. Roentgenol.*, **49**, 307.

Incision and Primary Suture of Abscesses of the Anal Region

By M. ELLIS, M.B., F.R.C.S.
Leeds

FROM time immemorial, the treatment of an acute abscess has been to incise and drain it. Granulation tissue grew in from the walls of the cavity and eventually filled it. The skin grew over the granulations and the incident was closed. It was considered essential that the cavity should fill in evenly without pocketing or the abscess might recur or a fistula form. In large abscesses around the anus, this pocketing was prevented by packing the cavity with gauze. As the abscess filled in, the pack was changed—often such a painful procedure that an anæsthetic was required. In any event, in an abscess of this size it was often weeks before healing took place. Antibiotics did not cure an established abscess nor expedite healing. Many years ago, when penicillin became available, I observed that if it had been given for some days in the vain attempt to cure the abscess the lesion appeared to heal more quickly after operation. I postulated the

theory that before operation the lining of the abscess had not only prevented infection in the abscess from getting into the circulation, but had also prevented penicillin in the circulation from getting into the abscess. At operation, the lining had been damaged and the penicillin already in the circulation had entered the abscess cavity, overcoming the infection and allowing quicker healing. Nearly ten years ago, I started operating on all abscesses on this principle. Pre-operatively a large dose of antibiotic was injected. Half to one hour later, at the peak of concentration of antibiotic, the abscess was incised, the pus and dead tissue were evacuated and the lining curetted to allow blood laden with antibiotic to ooze in. The antibiotic was expected to overcome the infection, so that primary suture could be carried out and healing obtained.

The following case shows the optimum result obtained by this treatment.

A man aged 45 presented with increasing pain and throbbing around the anus for six days. On examination, an abscess was discovered, so 100 mg terramycin was injected intramuscularly with the pre-anæsthetic. Forty minutes later under Pentothal and cyclopropane the abscess was incised. The cavity was about 2½ in. (5·5 cm) in diameter. Pus was evacuated and the lining curetted. A large stitch then completely encircled the cavity so that on tying it was completely obliterated. On the fourth day, when the sutures were removed, the wound edges were in firm apposition. On the seventh day, the wound remained healed and the patient went back to heavy work. He had been treated as an out-patient and there was no recurrence.

Experience over the years has shown that certain factors can delay or prevent the rapid primary healing obtained in this case:

(1) *Skin necrosis.*—If conservative treatment is continued until the abscess points through the skin, this skin may slough. The firm sutures obliterating the cavity will cut through this skin, leaving a superficial ulcer, which may prolong healing by as much as two weeks.

(2) *Inadequate evacuation of the abscess.*—All loculi must be discovered, evacuated and curetted. If one loculus is left, it will grow into a new abscess. All slough must be evacuated.

(3) *Inadequate suturing.*—The abscess cavity must be completely obliterated by the sutures. Failure to do this will allow the dead space to fill with blood which may become the focus of new infection when the antibiotic is discontinued.

(4) *Large pelvi-rectal abscesses* in which the roof of the cavity is beyond the reach of the finger. Such cavities are almost impossible to obliterate.

In a series of 200 consecutive cases, the incidence of these factors will be discussed. Of these cases, 13 had perineal, 109 perianal and 78 ischiorectal abscesses.

Perineal abscesses, 13. 11 male, 2 female. 11 healed within seven days, 1 in eight to twelve days and 1 in over twelve days. Gaping of the wound occurred in the last two cases after the sutures were removed; possibly the sutures were not firm enough. 12 abscesses were due to staphylococci and one, which healed in seven days, to *B. coli*.

Perianal abscesses, 109. 79 male, 30 female. These abscesses were often of considerable size, often multilocular, and the cavity sometimes encircled the anus posteriorly. After evacuation of the contents, the ischiorectal fascia, shutting off the fossa, was always found to be intact.

Among 85 patients healing in seven days, one was notable. She was 38 weeks pregnant, with an abscess 1½ in. (3·8 cm) in diameter. About a week after being discharged healed, her baby was delivered without the wound breaking down.

In the 24 patients not healed by seven days 14 were healed in eight to twelve days and 10 in over twelve days. Skin necrosis at the operation was noted in 9. One case was badly sutured and the wound gaped widely on the fourth day when the stitches were removed. In only one patient, a young man, was a chronic fistula left. One old woman developed a fistula a few weeks after operation which quickly flared up into another abscess. When this was opened, a piece of nylon suture was found and removed; the cavity was curetted, primary suture was carried out and there was no recurrence. Similarly in an old woman who had an ischiorectal abscess, it would appear that the nurse cut away the knot from the deep mattress suture and allowed it to remain in the tissues.

The type of organisms in the pus, 60% staphylococci, appeared to play no part in delaying healing.

Ischiorectal abscesses, 78. 53 male, 25 female. In these cases an opening in the ischiorectal fascia was discovered leading into a cavity of varying sizes alongside the anus. In 55 healing was complete in a week, 8 healed in eight to twelve days and 11 in over twelve days. In the 19 cases with delayed healing, 7 had skin necrosis, and a loculus was missed in 1. In the remainder, the wound gaped after the sutures had been removed, suggesting poor suturing. There was 1 case of chronic fistula. Staphylococci occurred in 36% and did not appear to delay healing.

Of the 4 cases classed as complete failures, 2 were large pelvirectal abscesses, in which the cavity was not obliterated, the wound suppurated and broke down widely. The third was an old woman from whom large sloughs were evacuated at operation and further sloughs occurred later. The fourth broke down on the eighth day in a moderately severe undiagnosed diabetic.

Skin Level Loop Colostomy

By Austin E. Wheatley, F.R.C.S.

London

In 1951 Patey read a paper entitled "Primary Epithelial Apposition in Colostomy". Later that year Butler (1952), in his Presidential Address, spoke of how he sutured the colon to the skin when fashioning an end colostomy. Since then suturing of the epithelium of the bowel to the skin has found acceptance and several papers have appeared about its use in performing a terminal colostomy.

Although Patey had recommended this technique in a loop colostomy it does not appear to have enjoyed widespread acceptance. Although I was familiar with the technique of skin apposition in end colostomy it was not until I visited Turnbull at the Cleveland Clinic, Ohio, that I saw this method applied to loop colostomy (Turnbull, 1958). To the best of my knowledge there are few who use it and as I feel that the advantages are many, I report upon my experiences.

A loop colostomy is usually performed for the relief of obstruction or to defunction the bowel because of inflammatory disease or to protect a colonic anastomosis. It is often a temporary measure and when the disease has been resected the colostomy is closed. If the colostomy is to be permanent it must have a satisfactory stoma; if temporary, it must relieve obstruction or defunction the bowel adequately, and must be easy to close.

The usual loop colostomy involves holding a loop of bowel on to the abdominal wall with a glass rod passed through the mesentery and a Paul's tube or catheter is tied into the bowel for decompression. However, it is common to find this tube clogged with fæces and failing to afford relief of the obstruction so that distension and colicky pain persist. A feature of this colostomy is the reaction that develops on the exposed serous surface of the bowel. The shiny serosa becomes œdematous and covered with exudate. Healing is slow, and the mucosa comes into apposition with the skin by retraction and scarring. During this a sulcus forms between the skin and bowel where fæces collect and act as an irritant. This serositis tends to produce diarrhœa in a manner similar to the condition of ileostomy dysfunction described by Warren and McKittrick (1951), Crile (1954) and Brooke (1952). A result of this inflammation and scar formation is the tendency to stricture at the mucosal skin junction, and closure entails tedious dissection. The bowel ends cannot be easily sutured because they are friable and œdematous for weeks; and many surgeons therefore resect the bowel ends and close them intraperitoneally. In the early post-operative period the colostomy acts frequently and the patient soils the abdominal wall and requires many dressings. The bulk of the bowel usually precludes an appliance; in all an unsatisfactory and distressing arrangement.

The undesirable features of a loop colostomy may be avoided by the primary suture of skin and mucosa. Fig. 1 shows how the skin and serous surfaces are joined, the stoma is wide, and although the bowel is almost at skin level there is an adequate spur, which is the prerequisite of a good colostomy (Gabriel, 1948). If the bowel is opened at right angles to its long axis the divided longitudinal muscle will tend to pull the edges apart, helping in the diversion of the fæcal stream (Rafal, 1949). The edges of the bowel are sutured to the skin and a wide stoma is produced; although slight œdema may follow, the inflammatory reaction of the serosa is minimal.

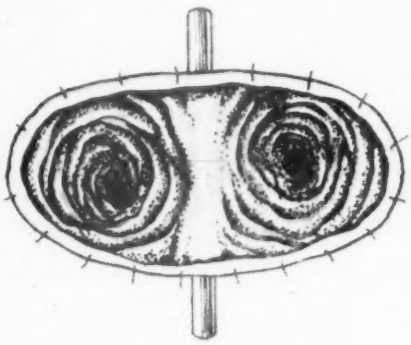

Fig. 1.—Diagram showing primary suture of skin to mucosa on either side of a thin glass rod. This also illustrates the wide stoma and efficient spur produced by this method.

Technique.—I prefer to make the colostomy through a separate incision, although there is no reason why it cannot be made through the initial wound. A piece of skin 2 in. long and ½ in. wide is excised, an elliptical incision gives better results than a linear one and there appears to be no disadvantage later when closing the colostomy. A loop of Paul's rubber tubing is brought through a hole in the mesocolon or sigmoid mesentery to permit easy handling of the bowel. The initial wound is closed, the bowel adjusted into position and a glass rod inserted through the mesentery

and the tubing removed. The rod is ¼ in. in diameter and 2½ in. long. This is adequate although narrower and shorter than usual. The bowel is opened transversely. In obstructed cases I have found that decompression at the time of laparotomy has many advantages. Exploration, assessment of the problem, the fashioning of a colostomy, and the closing of the abdomen are much easier when the bowel has been deflated. Having already emptied the bowel I have not been troubled in these obstructed cases by flooding and soiling of the wound with fæces while suturing the bowel to the skin, which is done with 00 plain catgut. A small cuff of rubber tubing is placed at each end of the glass rod to discourage it from slipping out of place. The suturing completed, the skin is cleaned, dried and painted with tinct. benzoin co. or Benzo-Mastiche. A Chiron bag with a 4 in. adhesive square suitably cut out is fitted over the colostomy, the bag being changed daily. Patients have had fewer unformed stools in the post-operative period, which I believe is due to the avoidance of the serositis. The nursing is much easier. The patient rarely undergoes the discomfort and misery of the orthodox loop colostomy. Healing is rapid and without inflammation or fibrosis. The rod may be removed on the fifth day, when the colostomy is soundly healed. The mucosa-skin junction becomes watertight quickly and there has been no infection of the wounds or peritoneum in my 14 cases. Neither has there been any retraction of the colostomies that have been left for long periods.

Finally, an important advantage is the absence of inflammatory reaction so that closure of the colostomy is easy. The mucosal skin junction is divided and the bowel can usually be freed by gauze dissection; it is surprising how bloodless this is. Suturing of the bowel is easier and, not being friable and inflamed, does not require resection.

Acknowledgments.—I wish to thank Messrs. Geoffrey Parker, D. M. Cooper, H. E. Lockhart-Mummery, and W. N. Van Essen upon whose patients I have operated, also Mr. R. Wellingham for the illustrations.

REFERENCES

Brooke, B. N. (1952) *Lancet*, ii, 102.
Butler, C. (1952) *Proc. R. Soc. Med.*, **45**, 41.
Crile, G. (1954) *Ann. Surg.*, **140**, 459.
Gabriel, W. B. (1948) The Principles and Practice of Rectal Surgery. 4th ed. London.
Patey, D. H. (1951) *Proc. R. Soc. Med.*, **44**, 423.
Rafal, H. S. (1949) *Amer. J. Surg.*, **77**, 507
Turnbull, R. B., Jr. (1958) *Surg. Clin. N. Amer.*, **38**, 1362.
Warren, R., and McKittrick, L. S. (1951) *Surg. Gynec. Obstet.*, **93**, 555.

Malignant Lymphoid Tumours of the Intestinal Tract [*Summary*]

By I. M. P. Dawson, M.A., M.D., M.R.C.P., J. S. Cornes, B.Sc., M.B., D.C.P., and B. C. Morson, M.A., D.M.

London

This paper summarizes some of the features seen in 38 patients with malignant lymphoid tumours of the intestine at the Westminster and St. Mark's Hospitals over the last twenty-five years and at the Gordon Hospital since its re-opening in 1947.

The series comprises 25 men and 13 women, having an average age of 55 years, and an age range from 16 to 83 years. In 29 the growths were single discrete tumours; in 4 there were two or more discrete growths and in 5 there was diffuse lymphoid polyposis involving a variable length of the intestinal tract. This last type, which forms 15% of our cases, is at present not well recognized.

Of the 33 cases with single or multiple discrete tumours, the jejunum was primarily involved in 3, the ileum in 9, the ileocæcal region in 3, the colon in 4 and the rectosigmoid in 14. Histological classification using carefully chosen criteria showed that 18 patients had lymphosarcomas, 15 reticulum cell sarcomas, 4 Hodgkin's disease and 1 a giant follicular lymphoma. There was no tendency for one histological type of tumour to produce multiple deposits or diffuse polypi, or to have a predilection for any one site. During our investigations we encountered a number of rectal lymphomas. These present as submucosal often polypoid swellings in the lower rectum and consist of aggregates of lymphoid tissue in the mucosa and submucosa. They contain follicles, do not invade muscle coats, and are usually separable on histological grounds from malignant lymphosarcomas, though there is a small group in which differentiation may be difficult. 80 such lesions have been described by Morson (1959).

Analysis of the major presenting symptoms and signs of the malignant tumours in our series shows that growths situated in the small intestine present commonly with nausea, vomiting and other signs suggesting intestinal obstruction;

a mass is often palpable. Growths in the colon and rectum most frequently present with bleeding and are often visible on proctoscopy or sigmoidoscopy. Those patients with lymphoid polyposis commonly have visible polypi in the rectum. In 14 of our 35 patients in whom presenting symptoms were adequately recorded, however, there was no complaint other than a feeling of malaise until the sudden onset of obstruction (11 cases) or perforation (3 cases) necessitated surgical intervention. In no case did a blood count at the time of operation show any evidence of lymphatic leukæmia.

At laparotomy 21 growths appeared as annular thickenings of the bowel, 11 as bulky tumours protruding into the lumen, 5 as diffuse polyposis and one as an aneurysmal dilatation of the bowel. The degree of lymph node enlargement seen at operation varied greatly and in our series bore no direct relation to the involvement or otherwise of the nodes by tumour. Many enlarged lymph nodes showed the changes of sinus catarrh only, while normal-sized ones were often involved in the malignant process; the presence of enlarged nodes is not necessarily an indication that the growth is inoperable.

33 cases were treated surgically and of these 17 subsequently had radiotherapy. 3 others had radiotherapy only, and 2 had no treatment. In our series post-operative radiotherapy did not materially alter the prognosis. 16 of the 38 cases are now dead; 11 died as a direct result of the disease, 2 more from immediate post-operative complications and 3 from unrelated causes. 3 more cannot be traced, leaving 19 survivors for follow-up. In the ten-year survival group there are 4 patients, all free of evidence of disease: all of them had lymphosarcomas. In the five- to ten-year group there is one patient who is known to have a recurrence; the remaining 14 patients have been followed up for less than five years. Of these, 5 have evidence of recurrence, while 9 are clinically free. Thus of 35 patients adequately followed up, 17 have either died of their disease or have already evidence of recurrence: it is probable that no more than one-quarter of all cases will survive ten years from the time of diagnosis.

We would like to plead for full recording and follow-up of all these tumours so that presenting symptoms and signs, type of growth, lymph node involvement, prognosis and the effects of treatment may be better assessed. A fuller report of this work will appear in the future.

REFERENCE

MORSON, B. C. (1959) *Postgrad. med. J.*, **35**, 101.

Meeting
March 9, 1960

MEETING AT THE MEDICAL COLLEGE OF ST. BARTHOLOMEW'S HOSPITAL, LONDON

THE following papers were read:

Radiotherapy in the Treatment of Advanced Carcinoma of the Rectum.—Mr. I. G. WILLIAMS.

Mercury Bichloride in the Treatment of Cancer of the Large Intestine.—Mr. W. M. KEYNES.

The Extra- and Intra-mural Blood Supply of the Colon.—Mr. J. D. GRIFFITHS.

Carcinomas of the Ovary Presenting as Ulcerating Tumours of the Rectum—Report of Two Cases and Review of Five Recorded Cases.—Dr. J. S. CORNES and Mr. HENRY R. THOMPSON. To be published in *Brit. J. Surg.*, July 1960, **48.**

Hirschsprung's Disease in the Adult.—Mr. IAN P. TODD.

The following demonstrations were given:

(1) **Rabbit's Ear Chamber to Show Tissue Reaction to Catgut.** (2) **Some Effects of Local X-irradiation on Healing.**—Professor D. SLOME, Dr. G. H. BLAIR and Mr. R. D. CHAMBERS.

Electron Micrographs to illustrate: (*a*) Fat Absorption in the Gut. (*b*) Effects of Radiation on Cells.—Dr. D. LACY and collaborators.

Leukæmia and Tumour Incidence in Control and Irradiated Mice.—Dr. PATRICIA LINDOP and Professor J. ROTBLAT.

Section of Surgery

President—RODNEY MAINGOT, F.R.C.S.

Meeting
April 6, 1960

The Blind Loop Syndrome

By JOHN BADENOCH, D.M., F.R.C.P.
Oxford

OVER one hundred years ago Thomas Addison published his classical description of pernicious anæmia, but although his careful clinical observations defined a picture which we still recognize to-day, he was quite unable to explain why the disease occurred. He states: "On examining the bodies of such patients after death I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences" (Addison, 1855).

By the turn of the century most clinicians were familiar with the natural history of the disease, and the knowledge that treatment was hopeless led to a renewed search for pathological changes which might lead to a discovery of the cause. In 1890, White, a physician at Guy's Hospital, searching for the ætiology of the anæmia, described 6 patients who had died and in whom the small intestine was found to be abnormal. One of these was a man with a stricture of the small intestine 12 in. (30 cm) above the ileocæcal valve. Five years later, in 1895, Faber reported a similar patient, this time with multiple strictures of the gut, and his findings led him to suggest that the anæmia might be due to the elaboration of toxins in the stagnant loops of bowel above the strictures. With increasing experience, it was recognized that macrocytic anæmia must be due to more than one cause. In 1929 Castle *et al.* showed that the prime defect in true Addisonian pernicious anæmia was lack of acid and intrinsic factor in the gastric juice. The results of their experiments made it possible to separate the patients with pernicious anæmia from the rest, but they left no doubt that there were other patients also with progressive macrocytic anæmia in whom the secretion of acid and intrinsic factor was preserved. In many of these, gross anatomical lesions of the intestine could be found. Gradually it became clear that any lesion of the intestine that produced stasis within the lumen of the gut could lead to the development of a syndrome characterized by macrocytic anæmia, loss of weight, and often diarrhœa and gross malnutrition—the clinical picture we have come to know as the blind loop syndrome.

The cause of the stasis is unimportant. Most of the early case reports were concerned with strictures of the jejunum or ileum or with reduction of the effective length of the bowel by the formation of short circuits or as a result of resection. However, in recent years we have learnt that diverticulosis of the upper small intestine can produce the blind loop syndrome if the condition is widespread and much of the bowel is involved (Taylor, 1930; Montuschi, 1949; Badenoch *et al.*, 1955).

I have now had an opportunity to study 8 of these patients. Most are elderly and have developed the diarrhœa and anæmia late in life. Colicky abdominal pain is common and difficult to relieve and in some of the patients intermittent diarrhœa has continued with little relief from treatment. Diagnosis may be very difficult for the diverticula may not fill with barium and their presence may not be suspected unless they can be detected radiologically.

As in other cases of anæmia due to the loop syndrome, improvement follows the use of antibiotics or resection of the area of bowel bearing the diverticula, and we believe that this is because the string of narrow mouthed sacs with their fetid contents exerts an effect very comparable to a length of bowel containing multiple strictures.

Finally, a similar picture can follow partial gastrectomy if gastroduodenal continuity is not preserved and an afferent loop is created. In some of these patients dilatation of the afferent loop and stagnation of its contents occur. In such cases organisms can be grown from the distended bowel and treatment with antibiotics will lessen the disturbance in intestinal function (Wirts *et al.*, 1959).

The clinical picture of the blind loop syndrome is variable. Loss of weight and diarrhœa are common. Many of the patients complain of abdominal pain and flatulence. Although diarrhœa is almost universal, steatorrhœa occurs in only about one-fifth of the cases, as Barker and Hummel (1939) have shown, and it tends to occur more commonly if the effective length of the bowel is reduced by resection than if the syndrome is due to the presence of strictures alone. When steatorrhœa does occur it may be followed by dangerous deficiencies, for example hæmorrhage due to hypoprothrombinæmia from

lack of vitamin K. Bleeding into the skin is the most common sign, but hæmaturia, melæna, or menorrhagia may occur and, perhaps most dangerous of all from the point of view of the surgeon, there may be massive retroperitoneal hæmorrhage simulating an acute intra-abdominal catastrophe. In others failure to absorb vitamin D and calcium leads to tetany and osteomalacia.

Patients who present with bruising or skeletal pain may have no other symptoms and in the absence of diarrhœa or abdominal distension the underlying cause is easy to overlook. Sometimes, however, the impairment of absorption of fat and other substances gives rise to multiple vitamin deficiencies, to asthenia and muscular weakness from loss of sodium and potassium, to hypoproteinæmia and œdema, and finally to a state of profound cachexia that may prove impossible to relieve even by heroic treatment.

Anæmia is common and may be the presenting symptom. Sometimes it is macrocytic and megaloblastic and indistinguishable from true pernicious anæmia, but usually it is the occurrence of a double picture in the peripheral blood in which some of the cells are macrocytic and hyperchromic, and others small and iron deficient, that arouses the suspicion that the symptoms may be due to a gastro-intestinal lesion. As in idiopathic steatorrhœa, the megaloblastic anæmia may well be the result of a combined deficiency of folic acid and vitamin B_{12}, but in the loop syndrome as Mollin *et al.* (1957) have shown, the deficiency of vitamin B_{12} is usually more important. For this reason it is dangerous to treat the anæmia with folic acid alone, for although the hæmoglobin may return to normal and the anæmia be cured, there is a very real danger of the development of subacute combined degeneration of the cord unless vitamin B_{12} is given at the same time.

Diagnosis

Patients with the blind loop syndrome can be divided into two groups. The first group, which we could call the surgical group, includes all those who have had an intestinal resection or a by-pass operation or indeed any intra-abdominal surgery at some time in the past. In these the occurrence of a megaloblastic anæmia combined with iron deficiency, or more important with free acid in the gastric juice, or the development of diarrhœa with fatty stools should at once arouse suspicion that the patient is suffering from the loop syndrome.

The patients in the second group, the medical group, in which the disease arises spontaneously, are even more difficult to diagnose. In these, if megaloblastic anæmia is the presenting symptom, differentiation from true pernicious anæmia may be very difficult, unless the secretion of acid in the stomach is preserved or the patient is younger than is usual in pernicious anæmia itself. If diarrhœa or steatorrhœa has brought the patient under supervision, confusion with idiopathic steatorrhœa may occur unless an anatomical lesion of the intestine can be demonstrated radiologically, unless occult blood is found in the stools or one of the screening tests, such as the absorption of xylose or radioactive iron, gives an unexpectedly normal result. If the diagnosis is in doubt, per-oral biopsy of the mucosa of the small intestine may be of assistance because the mucosa of the small intestine is often normal in the loop syndrome whereas in idiopathic steatorrhœa the characteristic blunting of the villi and loss of absorptive surface are found.

Whatever the cause of the blind loop syndrome, it is important that an accurate diagnosis be made, for without it the chance of a surgical cure will be denied even to those in whom radical relief is possible, and they may be condemned to a complicated medical regime for the rest of their lives.

REFERENCES

ADDISON, T. (1855) On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules. London.

BADENOCH, J., BEDFORD, P. D., and EVANS, J. R. (1955) *Quart. J. Med.*, **24,** 321.

BARKER, W. H., and HUMMEL, L. E. (1939) *Bull. Johns Hopk. Hosp.*, **64,** 215.

CASTLE, W. B., TOWNSEND, W. C., HEATH, C. W., and STRAUSS, M. B. (1929) *Amer. J. med. Sci.*, **178,** 748.

FABER, K. (1895) *Hospitalstidende*, p. 601.

MOLLIN, D. L., BOOTH, C. C., and BAKER, S. J. (1957) *Brit. J. Haemat.*, **3,** 412.

MONTUSCHI, E. (1949) *Proc. R. Soc. Med.*, **42,** 868.

TAYLOR, G. W. (1930) *New Engl. J. Med.*, **202,** 269.

WHITE, W. H. (1890) *Guy's Hosp. Rep.*, **47,** 149.

WIRTS, C. W., GOLDSTEIN, F., CALARESU, F. R., KRAMER, S., and CONCANNON, J. (1959) Proceedings of the World Congress of Gastroenterology. Baltimore; **1,** 451.

The Blind Loop Syndrome

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IN the previous paper, Dr. Badenoch has indicated the types of intestinal lesion which may be associated with the blind loop syndrome and he has stressed their relationship to megaloblastic anæmia and B_{12} deficiency. This paper describes the defects of intestinal function that may occur in the blind loop syndrome and indicates how these absorption defects may lead to

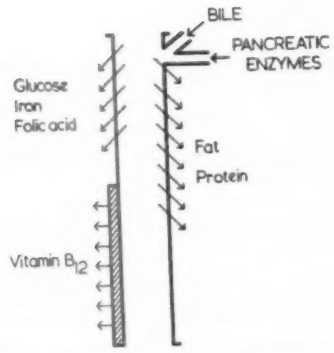

FIG. 1.—Sites of absorption in the small intestine.

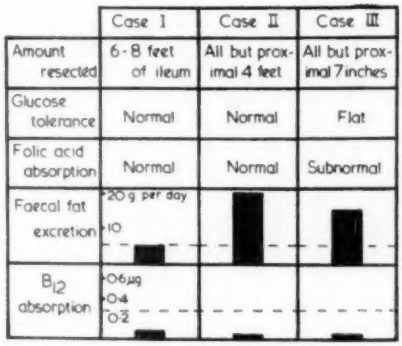

FIG. 2.—The results of glucose, folic acid, fat and vitamin B_{12} absorption tests in patients who had undergone resection of varying amounts of the distal small intestine (Cases I, II and III). In this and subsequent figures, the interrupted lines indicate the upper limit of normal fæcal fat excretion (6 g per day) and the lower limit of normal B_{12} absorption using a test dose of 1·0 µg (Mollin *et al.*, 1957).

deficiency states. The treatment is also discussed.

The pathogenesis of malabsorption and megaloblastic anæmia in jejunal diverticulosis will not be included in this paper, since this condition rarely requires surgical treatment.

Physiological Considerations

Fig. 1 illustrates diagrammatically the sites at which absorption of different substances appears to occur (Booth, 1960). Substances such as glucose, folic acid or inorganic iron, which require no digestion and are absorbed rapidly, are probably absorbed as soon as they reach the absorbing surface of the upper small intestine. Fat and protein require preliminary digestion by bile and pancreatic enzymes and they are absorbed more slowly; the rapid motility of the upper intestine propels them more distally before absorption is complete. The absorption of vitamin B_{12} is remarkable, for under physiological conditions it is only absorbed from the ileum (Booth and Mollin, 1959).

Effects of Intestinal Resection

Since B_{12} absorption occurs in the ileum, resection or disease of this area causes malabsorption of B_{12}. Whether an anatomical lesion of the intestine causes malabsorption of other substances depends on the site and extent of the lesion. This is illustrated first by the results of absorption tests in 3 patients subjected to resection of the distal small intestine (Fig. 2).

The first patient (Case I) had had 6 to 8 ft (2 m) of ileum resected. This caused malabsorption of vitamin B_{12}, but glucose, folic acid and fat, being absorbed proximally, were absorbed normally. In Case II the resection was more extensive, only four feet of the proximal jejunum remaining. Glucose and folic acid were normally absorbed but there was steatorrhœa in addition to malabsorption of vitamin B_{12}. In the third patient (Case III), the resection was so massive that there was not only malabsorption of B_{12} and steatorrhœa, but also interference with the absorption of glucose and folic acid (Fig. 2).

Malabsorption in these resection patients does not appear to be due to flooding of the remaining bowel with bacteria, for oral antibiotics are ineffective in improving absorption.

Blind Loop Syndrome

Intestinal absorption tests.—As in patients subjected to resection, the types of malabsorption in patients with blind loop syndromes depend on the site and extent of the lesion. However, it is likely that bacterial contamination of the small intestine plays the major part in causing malabsorption in these patients. There may be no actual loss of the absorbing surface of the small intestine, but the presence of the anatomical lesion appears to encourage the growth of an abnormal bacterial flora in the small intestine (Seyderhelm *et al.*, 1927; Girdwood, 1959) and this appears to be the factor that causes malabsorption (Badenoch *et al.*, 1955; Mollin *et al.*, 1957). Examples of the intestinal function tests in 3 patients are shown in Fig. 3.

The first patient (Case IV) had a stricture of the terminal ileum and there was only malabsorption of vitamin B_{12}. This situation is analogous to that seen after resection of 6 to 8 ft of ileum (Case I, Fig. 2) with the difference that in this case absorption improved to normal after a four-day course of Aureomycin (Fig. 3).

The lesion in the next patient (Case V) was more extensive. She had had two entero-entero anastomoses performed for tuberculous stric-

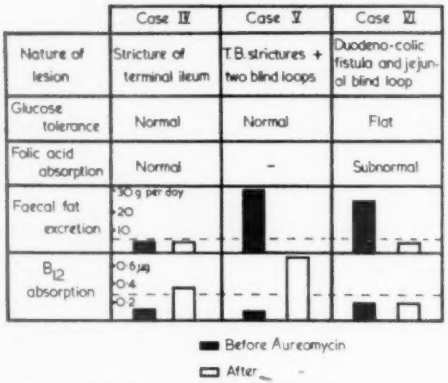

FIG. 3.—The results of similar absorption tests before and after antibiotics in patients with blind loop syndrome (Cases IV, V and VI).

tures and although the proximal few feet of her gut were radiologically normal, the distal intestine was very much dilated and contained several blind loops. She also failed to absorb B_{12}, but the more extensive lesion was associated with steatorrhœa. Glucose tolerance test, however, was normal. The absorption of B_{12} was temporarily improved by Aureomycin (Fig. 3).

The third patient (Case VI) had a duodeno-colic fistula and a large entero-entero anastomosis with an obstructed loop of jejunum. There was steatorrhœa and subnormal B_{12} absorption, but like the patient with the most extensive resection (Case III, Fig. 2) absorption of folic acid and glucose was also abnormal. The steatorrhœa improved after prolonged tetracycline therapy. In her case, however, B_{12} absorption remained subnormal after this treatment.

B_{12} deficiency in the blind loop syndrome.—Patients who have blind loops, strictures, or fistulæ involving the distal small intestine almost invariably fail to absorb vitamin B_{12} normally, for the ileum is flooded with bacteria derived either from stasis within obstructed loops or through fistulæ from the colon. It is therefore not surprising that the predominant and often the only deficiency occurring in these patients is a megaloblastic anæmia due to B_{12} deficiency (Mollin and Ross, 1954; Mollin, 1959). This may sometimes be severe enough to cause subacute combined degeneration of the spinal cord (Hurst, 1933; Wilkinson, 1955; Richmond and Davidson, 1958). Some years may elapse before B_{12} deficiency develops for, as after total gastrectomy, anæmia will only occur when the stores of vitamin B_{12} in the liver have been exhausted. The development of B_{12} deficiency in the patient with tuberculous strictures and blind loops (Case V, Fig. 3) is shown in Fig. 4.

Case V.—This patient first presented at Hammersmith Hospital in 1943 with tuberculous peritonitis. In 1944 and 1946 recurrent bouts of intestinal obstruction necessitated entero-entero anastomoses as life-saving procedures. She had diarrhœa following these operations and then, four years later, in 1950, developed a megaloblastic anæmia. This was associated with a subnormal serum B_{12} concentration (70 $\mu\mu$g per ml).[1] She was treated first with a single injection of 20 μg of vitamin B_{12} and there was an excellent reticulocyte response and rise in her red cell count (Fig. 4). For four years she continued to receive 40 μg of B_{12} monthly and since 1954 has been given 200 μg monthly. Apart from a recurrence of her intestinal tuberculosis in 1957 she has remained well without other treatment. Her diarrhœa has been controlled

[1] Normal range 140 to 960 $\mu\mu$g per ml (Mollin and Ross, 1957).

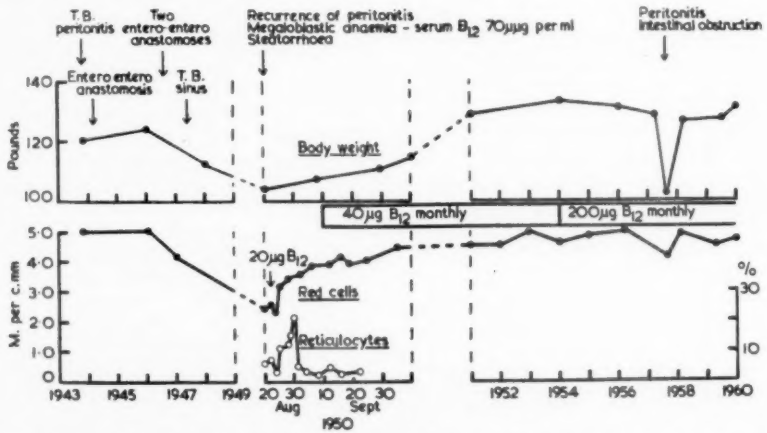

FIG. 4.—The changes in body weight, red cell count and reticulocytes in a patient with blind loop syndrome associated with tuberculous peritonitis, treated with vitamin B_{12} (Case V).

by a low fat diet and despite marked steatorrhœa she has no osteomalacia or evidence of any other deficiency. This is an example of a distal intestinal lesion causing a pure B_{12} deficiency state.

In this patient the megaloblastic anæmia was an incident during the course of prolonged and irreparable intestinal disease, associated with obvious intestinal symptoms and gross steatorrhœa. In contrast, patients with a localized lesion of the ileum may have minimal intestinal symptoms, and it may be the anæmia that first draws attention to an intestinal lesion. This type of presentation is illustrated by a patient who initially attended Hammersmith Hospital (Professor J. McMichael) with complaints of general malaise and shortness of breath (Case VII).

Case VII.—Her hæmoglobin was 9·6 g per cent and stained blood films showed macrocytes and signs of iron deficiency. Sternal marrow was megaloblastic and her serum B_{12} concentration (45 $\mu\mu$g/ml) was subnormal. She had occult blood in her stools. Since she had free acid in the gastric juice, it was unlikely that she had Addisonian pernicious anæmia, and for this reason attention was directed to the small intestine. A barium follow through (Dr. J. Laws) revealed gross dilatation of the terminal ileum which was interpreted as indicating chronic intestinal obstruction. After treatment with iron, vitamin B_{12}, and oral antibiotics, laparotomy was performed by Mr. R. H. Franklin who discovered a grossly dilated segment of terminal ileum. It was obstructed by a congenital vascular band a few inches proximal to the ileocæcal valve (Fig. 5). Resection of the stricture and end-to-end anastomosis was performed and the result has been excellent in this patient.

Effects of surgery.—Where possible, blind loops should be corrected surgically and the results are usually good provided that extensive resection is not required. The main operative hazard is often the associated malnutrition and patients who are severely undernourished are bad operation risks. For this reason preparation for operation is important. Anæmia and other deficiencies should be corrected and a preliminary course of oral antibiotics is advisable.

In some patients, such as those who have chronic adhesive tuberculous peritonitis, surgical correction may not be technically possible. However, as Fig. 4 shows, such patients may remain well if their anæmia is treated with vitamin B_{12} and they are given a low fat diet.

FIG. 5.—Operation specimen showing gross dilatation of the terminal ileum caused by a congenital stricture a few inches proximal to the ileo-cæcal valve (Case VII).

Blind Loop Syndrome with Intestinal Resection

Intestinal function tests.—Blind loops, stricture, or fistulæ may be complicated by intestinal resections. In patients with such lesions, the type of malabsorption depends on the extent of the resection which has been carried out. Two extreme examples are shown in Fig. 6.

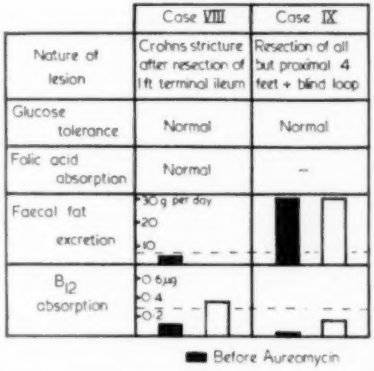

FIG. 6.—The results of absorption tests before and after antibiotics in patients with resection associated with stricture (Case VIII) and blind loop (Case IX).

The first patient (Case VIII) had only lost 12 in. (30 cm) of the terminal ileum but a stricture had occurred at the site of the anastomosis. Her malabsorption was predominantly due to her stricture for she failed to absorb B_{12} and this was corrected by Aureomycin.

In the second patient (Case IX) the resection was very much more extensive and only about 4 ft (120 cm) of the jejunum remained. A side-to-side anastomosis to the colon had been performed and as often happens after this operation, the terminal small intestine had blown up to form an enormous blind loop. However, the malabsorption in this patient was predominantly due to the resection, not to the blind loop, for in

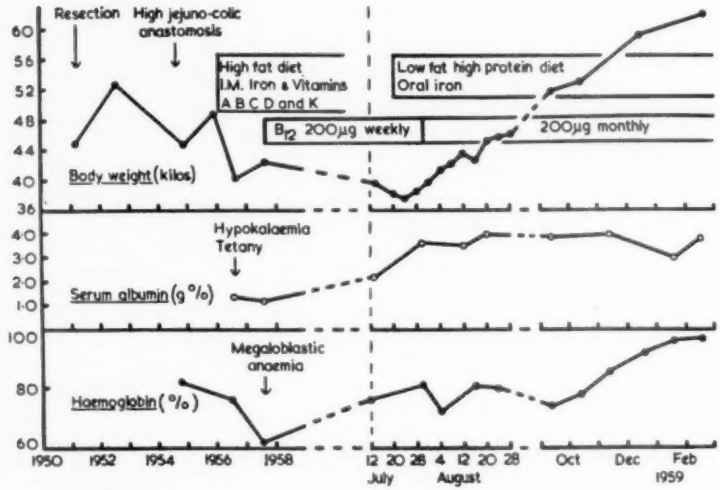

FIG. 7.—The changes in body weight, serum albumin and hæmoglobin in a patient with Crohn's disease (Case X), treated with a low fat diet.

contrast to the blind loop patients, no improvement in absorption occurred when Aureomycin was given (Fig. 6). In such patients surgery is not usually curative for the patient's resection itself often causes malabsorption (Fig. 2). Although the blind loop in this patient did not contribute to his malabsorption, it did cause anæmia from chronic blood loss. The mucosa of blind loops often becomes ulcerated and bleeds and in this case bleeding only ceased when the blind loop was corrected by further surgery.

Dietary management.—The commonest condition causing the mixed type of lesion, resection together with blind loops, is Crohn's disease. Vitamin B_{12} deficiency occurs almost inevitably in such patients and they usually require treatment with this vitamin (Meynell *et al.*, 1957). However, their diet is also important. A low fat diet is necessary if there is steatorrhœa, for large amounts of dietary fat may cause incapacitating diarrhœa. This is shown in Fig. 7, which illustrates the course of a patient with extensive Crohn's disease (Case X) whose clinical condition improved greatly when she was given a low fat diet.

Case X.—This patient first developed symptoms in 1950 and in early 1951 required a resection of the terminal ileum. In 1954, there was an extensive recurrence and a high jejuno-colic anastomosis was necessary, leaving approximately 4 ft (120 cm) of jejunum proximal to the anastomosis. After this operation she had severe diarrhœa, developed hypoproteinæmia and her legs became œdematous. By 1956 she was very ill and grossly undernourished. She was being treated with injections of iron and most of the vitamins, an injection of some sort being given every day of the week except Sundays during this time. In 1957 she developed megaloblastic anæmia and she was also given vitamin B_{12}. Throughout this period, however, she had been treating herself with a high fat diet in a vain attempt to fatten herself up. When the dietary fat was reduced in August 1958 she made a remarkable recovery. She now only requires one injection parenterally, vitamin B_{12} once monthly, and remains well.

Conclusion

Blind loop syndromes are less frequently encountered to-day, for surgeons are aware of the potential hazards of the entero-entero anastomosis or of side-to-side operations. In some patients, however, it may not be possible to avoid creating such lesions. If such patients have steatorrhœa, their diarrhœa may be controlled by a low fat diet, and if megaloblastic anæmia develops, they require vitamin B_{12}. Their anæmia should never be treated with folic acid alone for, as in pernicious anæmia, this may precipitate subacute combined degeneration of the cord (Best, 1959).

Acknowledgments.—We wish to thank the physicians and surgeons of Hammersmith Hospital who have kindly allowed us to study patients under their care. We are also particularly grateful to Dr. F. Avery Jones, Dr. N. F. Coghill and Dr. R. J. Harrison for their collaboration in the study of patients described in this paper.

REFERENCES

BADENOCH, J., BEDFORD, P. D., and EVANS, J. R. (1955) *Quart. J. Med.*, **24**, 321.
BEST, C. N. (1959) *Brit. med. J.*, ii, 862.
BOOTH, C. C. (1960) *Brit. J. Radiol.*, **33**, 201.
——, and MOLLIN, D. L. (1959) *Lancet*, i, 11.
GIRDWOOD, R. H. (1959) *Proc. R. Soc. Med.*, **52**, 37.
HURST, A. F. (1933) *Guy's Hosp. Rep.*, **83**, 47.
MEYNELL, M. J., COOKE, W. T., COX, E. V., and GADDIE, R. (1957) *Lancet*, i, 901.
MOLLIN, D. L. (1959) Lectures on the Scientific Basis of Medicine (Brit. Postgrad. Med. Fed.). London: **7**, 94.
——, BOOTH, C. C., and BAKER, S. J. (1957) *Brit. J. Hæmat.*, **3**, 412.
——, and ROSS, G. I. M. (1954) *Proc. R. Soc. Med.*, **47**, 428.
——, —— (1957) Vitamin B_{12} und Intrinsic Factor. I Europäisches Symposion, Hamburg. Ed., H. C. Heinrich, Stuttgart; p. 417.
RICHMOND, J., and DAVIDSON, L. S. P. (1958) *Quart. J. Med.*, **27**, 517.
SEYDERHELM, R., LEHMANN, W., and WICHELS, P. (1927) *Krankheitsforschung*, **4**, 263.
WILKINSON, R. W. (1955) *Lancet*, i, 74.

The Natural History of Achalasia of the Cardia [*Abridged*]

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THE natural history of achalasia of the cardia has been studied by tracing the progress of 85 unselected patients in whom the diagnosis was first established between 1933 and 1948. In 1958 33 of these patients were found to be alive and were investigated clinically and radiologically. 24 were known to have died and the cause of death was established. Of the remaining 28 patients, 8 were untraced, 4 known to have died were excluded because the cause of death could not be established, and 16 were excluded because of uncertainty in the diagnosis of achalasia.

Patients No Longer Alive (24)

Duration of disease.—Fig. 1 shows the age of onset of the disease and its duration in the group of 24 patients who died from known causes. While those patients in whom the disease started at an early age failed to achieve their expectation of life by many years, a calculation of the expectation of life from the Life Tables of the Registrar-General of the remainder shows that the majority died before their expected age of survival. 5 patients exceeded their expectation of life.

Cause of death.—Of these 24 patients, 7 died

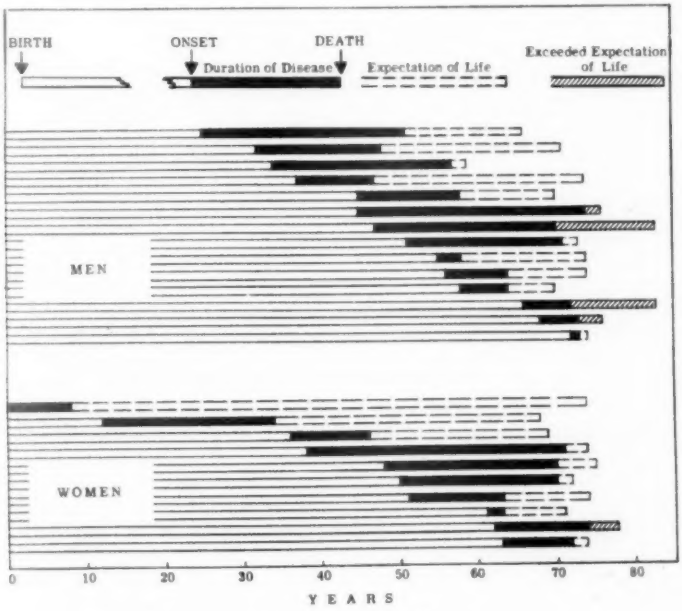

FIG. 1.—Duration of life.

following the development of carcinoma of the œsophagus in the presence of long-standing achalasia. The duration of achalasia at the time of death was between eight and thirty-three years. In all cases the presence of malignancy was proven histologically by biopsy or at autopsy. There were 5 men and 2 women. Despite treatment, all had gross dilatation of the upper segment at the time of discovery of malignant change. The diagnosis of malignant change was established only after extensive local spread or metastases had occurred and only palliative treatment was possible. Delay in the recognition of malignancy occurred because: (1) The patients were accustomed to episodes of dysphagia from their achalasia and did not seek advice until the dysphagia became severe. (2) Considerable extension of the growth occurred before it obstructed the passage of soft foods (which these patients usually take) through the grossly dilated œsophagus. (3) There is difficulty in the radiological detection of a carcinoma in the presence of a dilated œsophagus often with a large residue of semisolid food producing multiple filling defects.

In the 24 patients in whom the cause of death was known this study established that carcinoma of the œsophagus was present in 29% at the time of death. If the 8 patients who were untraced and the 4 patients who had died from unknown causes were all assumed to have died and to have been free of malignancy then a minimal incidence of 7 cases of carcinoma in 36 cases of achalasia (19%) is established.

While there are many records of isolated cases of carcinoma of the œsophagus complicating achalasia of the cardia, only a few authors give incidence rates. The latter vary from 1·5% in an unstated number of cases (Hoover, 1945) to 9% in 33 cases (Kornblum and Fisher, 1940). The incidence of malignancy in the present study is the highest recorded. The features of malignant change in this group are similar to those in 27 cases discussed by Williams (1956) in that men preponderated, achalasia had been present many years, and the middle third of the œsophagus was most frequently affected. In the present state of knowledge chronic retention of œsophageal contents cannot be excluded as a factor contributing to malignancy and effective surgical drainage should be established early in the disease.

5 of the remaining patients died in a cachectic state. 2 of these failed to survive gastrostomy and one died while awaiting this operation. These patients reached hospital in a state of advanced dehydration and failed to tolerate surgery. Apart from one patient who died following œsophagogastrostomy, the remainder of these 24 cases who died with achalasia of the cardia had other conditions which were considered to be the main causes of death. These included 5 patients with malignant disease in sites other than the œsophagus, 3 with pneumonia (which may have resulted from inhalation of œsophageal contents), and 3 with miscellaneous conditions.

Patients Still Alive (33)

Progress of the disease.—The age of onset and the duration of the disease at the time of interview in 33 patients who were still alive is shown in Fig. 2. The minimum duration of the disease was ten years. In 14 patients achalasia had been present from twenty to forty-five years. While the clinical features at the time of interview were assessed as accurately as possible, the capricious nature of the disease, the episodic variation in the severity of symptoms, and the lack of knowledge of past details of their illnesses on the part of some patients made it possible only to report on the outstanding features of these cases. However, the information was sufficient to allow evaluation of the natural history of the disease.

Early in the investigation it was apparent that there were periods of quiescence and exacerbation in the clinical picture. These appeared to be spontaneous in that they were unrelated to treatment or any other detectable cause. Such spontaneous variation is of importance in that assessment of the results of treatment of achalasia of the cardia may be inaccurate unless the patients are followed over the course of many years. Although comparison of consecutive radiographs showed dilatation of the œsophagus to be progressive in these patients, in the majority the clinical features were divisible into three readily recognizable stages.

Stage I—Onset.—The onset of the disease was sudden in most patients and was characterized by pain, dysphagia, and regurgitation. The pain was often intense and radiated from the substernal region into the neck and jaws. It was relieved by the onward passage of œsophageal contents or by forced regurgitation, and appeared to be due to distension of the œsophagus by retained contents. In a minority of patients the acute picture was absent and under these circumstances errors and delay in diagnosis were common. Some had been treated symptomatically for indigestion and had apparently improved. This improvement was spurious and was associated with the progression of the disease to Stage II. In those patients in whom the diagnosis was established at an early stage, conservative treatment was usually employed and was

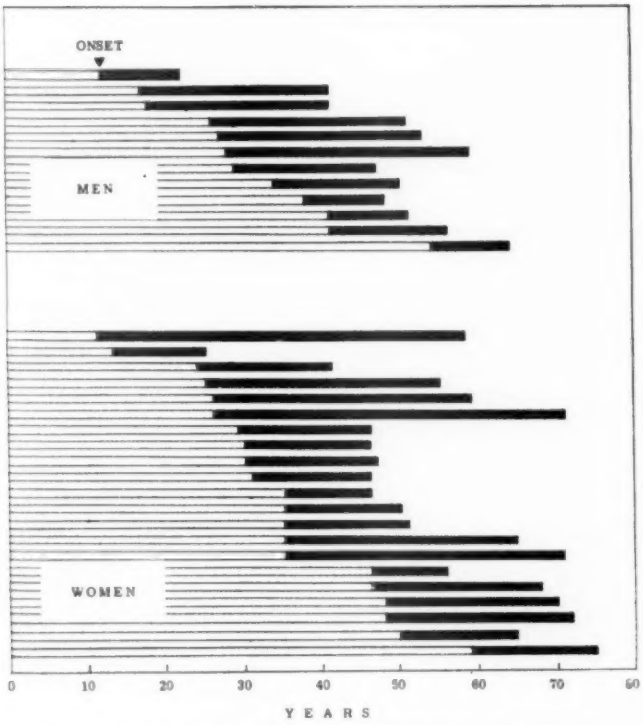

FIG. 2.—Age of onset and duration of disease at time of interview.

erroneously considered to be effective as the disease progressed to Stage II.

Stage II—The silent period.—With progressive dilatation of the œsophagus pain and regurgitation became less marked though intermittent dysphagia often occurred. This silent period ensued when dilatation of the œsophagus made it sufficiently voluminous to accommodate a normal meal without distension. At this stage the patients had often learned tricks to facilitate the onward passage of food through the cardia. These consisted chiefly of forced swallowing of air or large quantities of fluid when dysphagia occurred. Such tricks resulted in the passage of small amounts of food through the cardia while part of the remainder gradually gravitated into the stomach during the period before the next meal. In this way the majority of patients were able to avoid regurgitation and to maintain or even increase their weight. A period of general improvement in health was often apparent at this stage and was not unnaturally ascribed to treatment employed at that time.

Stage III—Progressive deterioration.—After many years relatively untroubled by symptoms other than dysphagia and occasional acute episodes of regurgitation (probably due to complete obstruction of the cardia by coarse food) most patients experienced a deterioration in health. This usually occurred after the disease had been present about twenty years, though in some cases it was longer. This deterioration was characterized not so much by a return of severe œsophageal symptoms as by weight loss, respiratory infection, and arthritic complications.

The weight loss appeared to be the result of malnutrition. Radiological surveys in such patients showed that they had gross œsophagectasia with considerable elongation and tortuosity of the upper segment. The dependent part of this segment often lay at right angles to the lower segment and in some cases an acute angle was formed at their junction. This kinking appeared to constitute an additional barrier to the passage of œsophageal contents and made the passage of bougies and dilators impossible. It may have been responsible for the increasing starvation of these patients producing further weight loss. Despite this, these patients were not troubled very much by œsophageal symptoms and in this showed marked contrast to the early stages of the disease.

In Stage III respiratory complications usually became troublesome. The lungs, having been subjected to repeated inhalation insults for many years, finally developed a decreased capacity for recovery from each episode and chronic pulmonary suppuration ensued. 11 patients (33%) suffered from major respiratory disease. Some of these were respiratory cripples and were so concerned with their breathlessness that they considered œsophageal difficulties of only minor importance.

Polyarthritis was seen in 5 patients (all women and all with achalasia of long duration). The arthritic changes affected small and medium joints and were clinically indistinguishable from chronic rheumatoid arthritis. In 2 patients joint disease led to complete inability to walk and to almost complete loss of use of the hands. All these patients with polyarthritis had extensive pulmonary suppuration. This suggests the possibility that arthritis is a tertiary effect of achalasia being directly related to pulmonary suppuration rather than œsophageal disease.

Radiological Changes

All patients were screened while swallowing barium and many had previous serial films for comparison. The oustanding feature of the radiological appearances was the inevitable progression of dilatation of the upper segment of the œsophagus despite treatment. Conservative measures were mostly without effect on this dilatation, though there was usually some improvement after cardiomyotomy (in 9 out of 16 cases). Gross œsophagectasia appeared capable of development in as little as ten years after the onset of symptoms.

In the assessment of the progress of achalasia of the cardia and in the evaluation of therapeutic measures, radiological appearances are of much greater value than clinical features since the latter may be deceptively minor in their nature (Stage II—above) despite gross œsophageal changes. Gross œsophagectasia is usually finally associated with marked malnutrition and crippling complications. Only palliative measures are of use at this time since dilatation of the cardia is impossible and cardiomyotomy, even if the patient is fit enough to withstand operation, is only of limited value.

For these reasons, where conservative treatment is employed in the early stages of achalasia of the cardia, a critical radiological assessment of the results should be made at least once a year. Progressive œsophageal dilatation is an indication for cardiomyotomy and if performed before gross œsophagectasia ensues, this operation should have considerable permanent beneficial effect.

Acknowledgments.—I am grateful to the several members of the staff of Guy's Hospital who kindly allowed me access to their patients for the purposes of this study.

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REFERENCES

HOOVER, W. B. (1945) *Surg. Clin. N. Amer.*, **25**, 707.
KORNBLUM, K., and FISHER, L. C. (1940) *Amer. J. Roentgenol.*, **43**, 364.
WILLIAMS, J. L. (1956) *Thorax*, **11**, 268.

The Surgical Management of Patients Who Have Received Corticosteroids
[*Abridged*]

By J. E. LENNARD-JONES,[1] M.B., M.R.C.P., and H. R. I. WOLFE, M.S., F.R.C.S.

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IN general, two types of patient are given corticosteroids. Some require corticosteroids in a physiological dose, usually between 25 and 50 mg of cortisone a day, to make good a deficiency due to the loss of their own adrenal glands. Others are given large pharmacological doses of these drugs as treatment for a disease. Unfortunately, suppressive treatment with cortisone-like drugs may upset the body's normal regulating mechanism whereby the adrenal glands increase their output of hormones in response to stress. Failure of the adrenals to respond to stress may also occur after treatment with corticotrophin (Hayes and Kushlan, 1956). Patients who have no adrenals and those whose adrenals have atrophied during treatment with corticosteroid drugs are alike in needing extra cortisone to prevent possible circulatory collapse at a time of stress, such as during and after an operation. Adrenal collapse is the only complication likely to be encountered among those maintained on doses of corticosteroids in the physiological range. Patients treated with large pharmacological doses are liable to many complications: infection which may spread unnoticed, metabolic disturbances, mental breakdown, and

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possibly venous thrombosis. Experimental work now seems to indicate that these drugs do not impair wound healing unless the body is lacking in protein (Thorn *et al.*, 1954, pp. 88, 106).

In an attempt to discover whether surgical success in ulcerative colitis is jeopardized by pre-operative cortisone therapy, one of us, in collaboration with Dr. Ewart, has studied the results of one-stage ileostomy and subtotal colectomy between 1951 and 1959 in a consecutive series of 131 patients with ulcerative colitis treated at St. Mark's Hospital. Our findings are summarized in this paper and will be presented in detail elsewhere (Ewart and Lennard-Jones, 1960). We have compared the surgical results in 52 of these patients, who had been treated with corticosteroids during the year before operation, with those in the remaining 79 patients who had not been so treated. Of the patients given corticosteroids, 31 were treated up to the time of operation, nearly half of them in a dose equivalent to 200 mg of cortisone a day or more. Since both the treatment groups contained patients with illness of differing severity, we have divided the patients into 4 sub-groups according to the severity of their illness as shown in Table I.

TABLE I.—CLASSIFICATION OF PATIENTS WITH ULCERATIVE COLITIS ACCORDING TO THE SEVERITY OF THEIR DISEASE

Group	General condition	Colitis	Reason for surgery	Urgency
A	Good	Chronic inactive	Disablement or local complications	None
B	Good	Mild active	Disablement or local complications	None
C	Poor and/or	Severe active	Failed medical treatment	Early
D	Critically ill	Very severe	Acute complications or rapid deterioration	Emergency

Groups A and B can be regarded as "good risk" and Groups C and D as "poor risk" patients. The number of patients and the results in each group are shown in Fig. 1. It can be seen that: (*a*) There was a higher proportion of mildly ill patients at the time of operation among those who had not received corticosteroids. (*b*) In each group, the mortality was approximately equal whether patients had received corticosteroids or not. There was only 1 death among 73 patients who were not severely ill. (*c*) The incidence of complicated recovery, defined by the occurrence of any complication, was equal whether patients had received corticosteroids or not.

Our detailed findings suggest that individual complications were rather more common among those who had received corticosteroids, and that these patients were detained in hospital a little longer than those untreated with these drugs. The incidence of pre-operative perforation of the bowel was apparently unaffected by corticosteroids. At operation, however, the bowel was torn rather more often in those who had received this treatment. The consequences of bowel perforation were often disastrous but they were the same in the steroid and non-steroid groups. Peritonitis caused more than half the deaths in the whole series and, in every case save one, it followed perforation of the bowel. Peritonitis was also the commonest cause of circulatory collapse, and on three occasions patients untreated with corticosteroids developed shock on this account without any signs in the abdomen suggesting the presence of generalized peritonitis. No case of unequivocal adrenal collapse occurred in this series. Two patients, one of whom had received corticosteroids and the other not, collapsed inexplicably after operation.

We have found no obvious correlation between the dose or duration of pre-operative corticosteroid therapy and the surgical result. 15 of the 31 patients treated with corticosteroids up to the time of operation became worse during the treatment and 7 improved a little. Of those who became worse, surgery was delayed on 3 occasions until the patients were desperately ill; 2 of them died and the recovery of the third was delayed by sepsis.

Taken overall, the patients who had received corticosteroids fared a little worse (Table II) than those who had not received these drugs. Some of the difference can be ascribed to the larger proportion of mildly ill patients in the non-steroid group. The mortality in this series depended more on the pre-operative condition of the patients than on whether they had received corticosteroids or not.

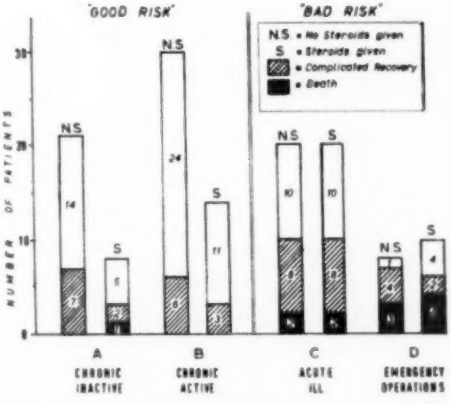

FIG. 1.—The results of surgical treatment in patients with ulcerative colitis of differing severity (St. Mark's Hospital, London).

TABLE II.—SURGICAL RESULTS IN ULCERATIVE COLITIS AMONG PATIENTS UNTREATED WITH CORTICOSTEROIDS AND AMONG PATIENTS TREATED WITH THESE DRUGS DURING THE YEAR BEFORE OPERATION

The overall mortality is correlated with the pre-operative condition of the patients and the severity of their disease

	No corticosteroids	Pre-operative corticosteroids
No. of patients	79	52
Deaths	5 (6%)	7 (13%) $P=0.1$
Complicated recovery .. * ..	25 (32%)	15 (29%)
Days in hospital after operation (Mean and S.D.)	28±10	34±18

Mortality among 73 "good risk" cases = 1 (1%)
Mortality among 40 ill patients = 4 (10%)
Mortality after 18 emergency operations = 7 (39%)

In order to determine the results of surgical treatment in peptic ulcer perforating during corticosteroid therapy one of us (H. R. I. W.) examined the case histories of all perforated ulcers treated surgically at University College Hospital and The Hospital for Tropical Diseases between January 1951 and December 1959. Of a total of 125 patients, 8 were being treated with corticosteroids when the perforation occurred. The whole series has been subdivided into two groups according to the patient's pre-operative condition, a "good risk" group and a "bad risk" group. The surgical results among those treated with corticosteroids have been compared to the results among those untreated with these drugs (Fig. 2). Although the numbers are small, the surgical results do not appear obviously affected by corticosteroid treatment.

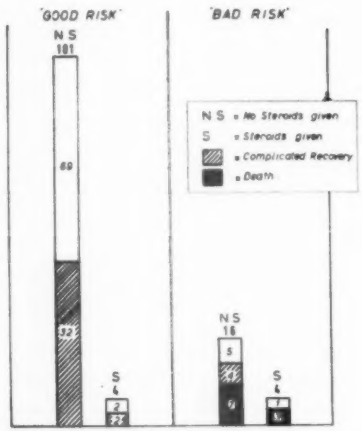

FIG. 2.—The results of surgical treatment in perforated peptic ulcer (University College Hospital and Hospital for Tropical Diseases 1951–1959).

Case IV, was known to have had an ulcer before treatment was started; 2 patients developed ulcer dyspepsia during treatment and 5 perforated without warning. The signs of perforation were frank in all but one case, a deaf and garrulous old lady who could not give a proper history but who presented as an acute abdominal emergency. No special difficulties were encountered at operation in any of the patients.

TABLE III.—CLINICAL DETAILS OF PATIENTS IN WHOM A PEPTIC ULCER PERFORATED DURING CORTICOSTEROID THERAPY

Case	Disease	Cortisone equivalent		Presentation of perforation	Pre-operative condition	Complications	Death
		Dose mg/day	Duration				
I	Local pemphigus	150	3 months	Suggestive	Good	Transient melæna	
II	Arthritis (?disseminated lupus)	75	9 months	Frank	Good	Superficial wound infection	
III	Dermatitis herpetiformis ..	200	11 weeks	Frank	Good	None	
IV	Lepromatous leprosy	175–125	15 weeks	Frank	Good	None	
V	Disseminated lupus erythematosus	150	8 months	Suggestive	Poor (congestive cardiac failure)	None	
VI	Lymphoma	300–1,000	4 weeks	Frank	Fair (Anæmia, leucopenia)	Circulatory collapse	+
VII	Myelomatosis	100	4 months	Frank	Poor (wasted, jaundiced, anæmic)	Peritonitis, burst abdomen	+
VIII	?Polyarteritis nodosa (carcinomatosis)	100	6 weeks	Suggestive	Very poor (circulatory collapse "moribund")	Circulatory collapse, peritonitis	+

The clinical presentation, morbidity and mortality among the 8 patients receiving corticosteroid therapy have been analysed in detail. 4 of the patients were in good physical condition at the time of operation and 4 patients were very ill (Table III); all had been treated with large doses of steroids for a long time. Only one, No serious post-operative complications developed among the 4 patients in good physical condition and none of them died. The remaining 4 patients were being treated with large doses of corticosteroids for lethal illnesses, all were very ill when the perforation occurred, and 3 of them died after operation. In Case V the signs of an

acute abdomen attracted attention though the patient was suffering from congestive cardiac failure and an acute pulmonary infection. Enormous doses of cortisone were needed to control the symptoms of the lymphoma from which Case VI was suffering; it is possible that he died because he was not given enough extra cortisone at the time of operation. Case VII was wasted, anæmic, leucopenic, jaundiced, had a low serum albumin, and was being maintained on continuous tetracycline therapy because of repeated chest infections. The last patient, Case VIII, had a pyrexia of unknown origin until the appearance in serial chest X-rays of pulmonary secondary deposits confirmed a clinical suspicion of carcinomatosis.

In addition to these 8 patients who were treated surgically, one patient who had received large doses of prednisone during the three months before perforation was managed conservatively. She was fat, breathless at rest owing to a long-standing pneumothorax and crippled by severe rheumatoid arthritis. She made an uneventful recovery with continuous gastric suction, antibiotics and additional hydrocortisone.

In summary, the presentation of the perforation in these patients was apparently unaffected by corticosteroid therapy. The mortality and morbidity appeared to depend on the preoperative condition of the patients and the disease from which they were suffering rather than on the steroid treatment.

Most diseases treated with corticosteroids are entirely a medical problem and the surgeon's advice is only sought when surgical complications are suspected, or when some intercurrent condition requires surgical treatment. In severe ulcerative colitis, however, we believe that physician and surgeon should co-operate in the management of the patient. Pre-operative medical treatment can adversely affect surgical results if an unsuccessful treatment is persisted with despite steady deterioration in a patient's condition. On the other hand, if, by medical means, a patient's condition can be improved before operation the likelihood of surgical success is increased. We suggest that corticosteroids used wisely may assist the surgeon in these circumstances.

Turning to the effect of corticosteroids on surgical diagnosis and assessment, the characteristic feature of a patient receiving large doses of corticosteroids is that he may not react in a way to which we are accustomed. Relief of pain, reduction of malaise with improved appetite, increased mental and physical activity, and fall in temperature may give a deceptive appearance of well-being when the patient is, in fact, dangerously ill. Our experience, and the reported experience of others, suggests that perforation of a peptic ulcer during corticosteroid therapy is usually frank. Perforation of the colon in ulcerative colitis is far less abrupt in its presentation and the diagnosis can be difficult in any patient; in the experience of one of us (H. R. I. W.) corticosteroids have possibly increased the difficulty.

Adrenal collapse can be avoided if patients who have received corticosteroid treatment during the previous eighteen months are given large doses of cortisone at the time of operation. A satisfactory regime is shown in Fig. 3. Cortisone given intramuscularly acts as a depot and is liberated slowly into the blood, so this route of administration should not be relied upon in an emergency. For rapid treatment hydrocortisone should be given intravenously. There is a real danger that a patient who has had corticosteroids

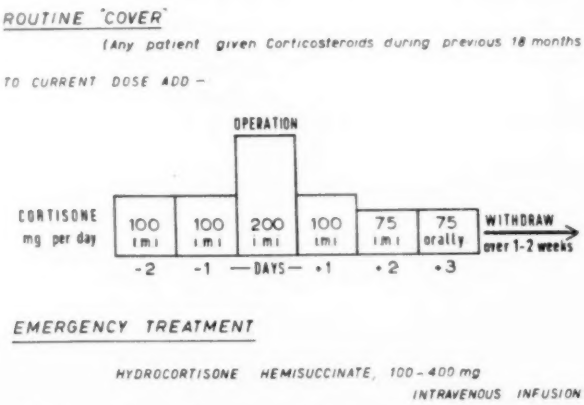

FIG. 3.—A regime of treatment for the prevention of adrenal collapse.

may be operated upon without cortisone cover because the surgeon and anæsthetist are unaware that he has had this treatment. Hospital notes at the present time do not bring corticosteroid treatment into sufficient prominence. Whenever these drugs are given, a calculated risk is taken and the notes should be distinctively marked so that all the relevant data are readily available to others. All patients given steroid therapy should be given a card stating the dose and drug prescribed and they should be told to show this card to doctors whom they consult. Before any patient has an operation the clinician must now find out whether he has received any treatment which might have been a corticosteroid drug.

It is possible that, under certain circumstances, corticosteroids increase the friability of the bowel wall in ulcerative colitis. One of us (H. R. I. W.) has found Brooke's (1959) method of decompression of the colon very valuable as it minimizes the danger of tearing the bowel during colectomy in severe cases of colitis. During the post-operative period, medical complications of corticosteroid therapy may develop and the presence of serious sepsis may be masked. It is as important for the surgeon to call in a physician at this stage as it is important for a physician to call in a surgeon when he is treating a severe case of ulcerative colitis. A patient receiving large doses of corticosteroids needs to be watched with special vigilance as small signs may be the only indication of serious disease.

To conclude, it is familiar experience that in patients who are very ill, particularly if they are apathetic, complications of their disease may develop without attracting attention. Patients treated with corticosteroids may appear deceptively well and complications of their disease may escape notice for this reason. Though our findings suggest that serious complications from corticosteroid therapy are not common during surgical management, it is necessary for the surgeon and anæsthetist to know when a patient has had this treatment. If small physiological doses are being taken, or treatment has been discontinued, it is only necessary to guard against adrenal collapse. If large pharmacological doses are being taken, adrenal collapse must be prevented and special watch must be kept for other complications.

Acknowledgments.—We are very grateful to the Consultant Staff of St. Mark's Hospital, the Hospital for Tropical Diseases, and University College Hospital for permission to study their records and to publish these results.

REFERENCES

BROOKE, B. N. (1959) *Lancet*, ii, 745.
EWART, W. B., and LENNARD-JONES, J. E. (1960) *Lancet*, ii, 60.
HAYES, M. A., and KUSHLAN, S. D. (1956) *Gastroenterology*, **30**, 75.
THORN, G. W., JENKINS, D., LAIDLAW, J. C., GOETZ, F. C., DINGMAN, J. F., ARONS, W. L., STREETEN, D. H. P., and MCCRACKEN, B. H. (1954) In: Medical Uses of Cortisone. Ed., F. D. W. Lukens. New York; Chapter 2.

A paper entitled **Complications of Achalasia** was read by Mr. DONALD BARLOW (London).

Section of Anæsthetics

President—J. ALFRED LEE, F.F.A. R.C.S., D.A.

Meeting
March 4, 1960

Post-operative Vomiting [*Abridged*]

By J. E. RIDING, M.D., F.F.A. R.C.S.

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SOME ten years ago there began to appear in the literature reports of the effects of dimenhydrinate and other antihistamines in the prevention and treatment of post-operative vomiting. Since then there has been a considerable revival of interest in this subject. This has been almost entirely concerned with the evaluation of anti-emetic drugs to the neglect of the more basic aspects of the problem. It is true that the latter have been investigated, but usually secondary to the main purpose—that of drug evaluation.

We still know little of the frequency and severity of post-operative vomiting in different circumstances and the various factors which may influence it. The ætiology is obscure, despite advances in the physiology and pharmacology of vomiting.

The basic principle underlying the investigation of post-operative vomiting is to compare the incidence, and sometimes also the severity, of sickness in two or more series of patients in whom different anæsthetic agents or drugs have been used. However, so great are the differences in detail in the methods by which this principle has been employed, that it is hardly ever possible to compare directly the results shown in the various reports.

For example—the definition of post-operative vomiting varies. Blumfield (1909) defined it as "any vomiting or retching occurring after the patient has recovered consciousness". Nausea was disregarded by him, and by many others before and since his day. There are difficulties in the measurement of a subjective response and nausea has often been ignored in the interests of objectivity. Retching, too, has often been disregarded. Since both nausea and retching are unpleasant and disturbing it would seem wiser to include these in the definition of post-operative vomiting. It cannot be assumed that patients classified as "not vomiting" have not suffered disturbing symptoms, nor can the assumption be made that nausea and retching will lead to vomiting. Burtles and Peckett (1957) drew attention to the fact that a patient may have no memory of sickness occurring shortly after operation. As Boulton (1955) also stressed, the common "emergence vomit" has to be taken into consideration. It is not sufficient for investigative purposes to record only those signs and symptoms occurring after the return of consciousness, since this point in time cannot always be decided by the observer, and the patient's memory may be misleading.

It is wiser therefore to define post-operative vomiting as "any nausea, retching or vomiting occurring after the end of the operation, whether remembered or not". Any less stringent definition is likely to result in the underestimation of sickness after operation.

Groups used for comparisons.—In most studies sickness has been recorded in unselected series of patients, no attention being paid to variables such as sex or the surgical procedures involved. The belief is, presumably, that in large series of patients these variables are equally represented but this is doubtful. Although the overall value of an anti-emetic drug can be demonstrated according to the criteria of sickness more precise information in specific circumstances is less easy to obtain. It is easier and quicker to use unselected large series but less easy to obtain for comparison closely similar groups of a useful size. Data of this type have been used in endeavours to assess the importance of factors influencing sickness but have often led to the comparison of dissimilar groups.

The use of closely similar series of patients, where efforts have been made to rule out variables, has been rare. Good recent examples are the reports by Phillips *et al.* (1958, 1960). The building up of such series is a much more tedious process, except perhaps in special surgical units, where substantial numbers of patients undergo similar operations under standard anæsthetic techniques. There is, however, no other way to obtain a clearer understanding of post-operative vomiting and of the factors influencing it.

Manner of observation.—Recently the recovery room has been used to facilitate the direct observation of sickness in patients after operation. This is obviously a great advantage, although it is not available to many investigators.

A common practice is to interview patients the day following operation, and to supplement this information with notes taken by specially instructed nurses. This is not ideal and may lead

to under-estimation of sickness, particularly by an inexperienced interviewer, but is often the only method available, and was used in the investigation to be described.

Classification of post-operative sickness.—A bewildering variety of classifications has been used. Complex classifications have not proved of great value; it is enough to record +ve or −ve according to the chosen criteria of sickness. To measure the severity as well is a different matter and classifications based, for example, on the duration of sickness, and on the number of vomiting episodes, have been used. The usual difficulty is that, whereas χ^2 tests of statistical significance can be applied to the proportions of patients having sickness in differing series, the examination of the qualitative results in this way is less easy. The demonstration by Bellville *et al.* (1959) that significance tests can be applied to the qualitative results is a most important recent advance in the study of post-operative sickness. Statistical tests to demonstrate the validity of results are not yet universally used; they are probably too often applied to the results of series which are not properly comparable. Perhaps the earliest use was by Mushin and Wood (1944), followed by Gordh and Rydin (1946).

Use of drugs.—The majority of recent studies have been concerned with the evaluation of anti-emetic drugs, when it is necessary to compare the sickness in treated and untreated groups of patients. This is sometimes done by observing, over a period of weeks or months, the incidence in untreated patients, in order to form a control series. Following this the routine administration of the drug to be tested over a similar period enables the incidence to be obtained in a treated series.

Others have administered the test drug to alternate patients. More recently the drugs to be tested and an inert placebo have been placed in indistinguishable ampoules, coded so that their contents are unknown to those taking part in the trial. The selection of patients for the administration can be made by reference to tables of random numbers. In addition to this the injection is frequently made while the patient is under anæsthesia. The nature of the solution given to a particular patient is not disclosed until the completion of the trial. In this way bias towards a desired or anticipated result can be avoided.

From this brief survey it can be seen that there is not yet a generally agreed detailed method of investigating post-operative sickness, so that it is perhaps not surprising that our views of this subject are largely based on a mixture of clinical impressions and the results of uncontrolled investigations.

My personal interest in this subject was aroused by the work of Jaquenoud and Mercier (1951, 1952) on the prevention of post-operative sickness by anti-histamines. They found that when any of several anti-histamines was added to the standard morphine-hyoscine premedication a reduction in the incidence of sickness occurred. Using hyoscine alone, and omitting both morphine and anti-histamine a diminution in incidence occurred of a roughly similar degree. This suggested that morphine in premedication is a likely cause of sickness after operation.

It seemed worth while to investigate this, since it appeared to be one of the possible influencing factors which are capable of modification, unlike, for example, the site of the operation. In addition it was decided to investigate the influence of atropine given pre-operatively since there was some doubt concerning its anti-emetic activity.

Desiderata.—It was thought best to study the effects of various combinations of dosage of morphine and atropine in series of patients as similar as possible.

The principal requirement was therefore large numbers of patients of the same sex, having an operation of a standard type in standard ward conditions. It was necessary to choose an anæsthetic technique which would allow wide variations in the drugs used for premedication. It was essential that morphine would not be required post-operatively.

Method.—The investigation was therefore carried out at a unit dealing with patients suffering from abortion. The operation for the evacuation of the uterus is of a standard type and duration.

Thiopentone was used as the sole anæsthetic agent. In this way the variable factor of the skill necessary to achieve smooth administration of inhalational anæsthetic agents was avoided. With this agent atropine could be omitted from premedication and emergence vomiting was very rare. The dose was 300–500 mg in most cases.

The operations were performed at the same hour each day and the same post-operative regime regarding food and drinks followed.

A preliminary trial showed that the incidence of sickness following operation when atropine 0·6 mg was used was appreciably lower than that observed when morphine 10 mg and atropine 0·6 mg had been used.

It was then decided to extend the trial to 12 series of patients, each series receiving one of the following premedications: Morphine 5·0 mg and 10·0 mg were each used alone. Each of these was combined in turn with atropine 0·3 mg, 0·6 mg, and 1·2 mg. In a further three series these doses of atropine were used alone. Normal

saline 1 ml was used as an inert premedication in a further series.

The administration of these drugs before operation by an "unknowns" technique was not possible because the surgeon in charge did not approve the use of drugs unknown to any of the staff. The best compromise proved to be that the sister in charge administered the premedicant combinations in rotation, leaving the anæsthetist and the assessor in ignorance of the drugs given to particular patients.

The patients were all personally interviewed on the day following operation, and all nausea, retching and vomiting, however trivial, were taken into account. Table I shows the size of each series. Table II shows the proportion of each having nausea, retching and vomiting.

TABLE I.—THE DRUGS USED IN PRE-ANÆSTHETIC MEDICATION IN TWELVE SERIES OF PATIENTS WITH NUMBER OF PATIENTS IN EACH SERIES (Total 870)

	No atropine	Atropine 0·3 mg	Atropine 0·6 mg	Atropine 1·2 mg
No morphine	76*	73	113	66
Morphine 5·0 mg	60	66	50	59
Morphine 10·0 mg	87	51	108	61
Total	223	190	271	186

*Saline 1·0 ml given as inert injection.

TABLE II.—PERCENTAGE NAUSEA, RETCHING AND VOMITING IN EACH SERIES

	No atropine	Atropine 0·3 mg	Atropine 0·6 mg	Atropine 1·2 mg
No morphine	22·4*	17·8	11·5	3·0
Morphine 5·0 mg	38·3	28·8	24·0	10·2
Morphine 10·0 mg	66·7	39·2	35·2	26·2

*Saline 1·0 ml given as inert injection.

It was found that following the standard morphine 10 mg and atropine 0·6 mg, sickness was reported by 35·2% of the patients. When atropine 0·6 mg was used alone the incidence was 11·5%—a significant difference. Morphine 10 mg alone was followed by an incidence of 66·7% which was significantly greater than after morphine 10 mg and atropine 0·6 mg. When neither atropine nor morphine was used the incidence was 22·4%—significantly greater than the incidence after atropine 0·6 mg alone.

Put in another way: When no premedication was given, sickness occurred in about one-quarter of the patients in the series. The incidence was halved by the use of atropine 0·6 mg and trebled by morphine 10 mg alone. Atropine 0·6 mg when combined with morphine 10 mg almost halved the incidence seen after morphine 10 mg alone.

The apparent tendency for the proportion of sick patients to increase as the dose of morphine increased whether atropine was given or omitted was confirmed by the application of χ^2 tests. Increasing the dose of atropine decreased the proportion of sick patients whether morphine was given or not. Again χ^2 tests support this finding. Table III shows the percentage of

TABLE III.—PERCENTAGE NAUSEA AND RETCHING IN EACH SERIES

	No atropine	Atropine 0·3 mg	Atropine 0·6 mg	Atropine 1·2 mg
No morphine	13·2*	2·7	2·7	3·0
Morphine 5·0 mg	16·7	9·1	10·0	1·7
Morphine 10·0 mg	14·9	11·8	12·0	11·5

*Saline 1·0 ml given as inert injection.

patients in each series who had nausea or retching only but who did not vomit. The effect of atropine alone was quite marked, compared with the incidence of nausea and retching observed after saline premedication, although atropine 0·3 mg appeared to have the same effect as atropine 1·2 mg. In the presence of morphine, atropine did not alter the incidence of nausea and retching greatly, except when a large dose of atropine (1·2 mg) was combined with a small dose of morphine (5·0 mg). Table IV shows the percentage of each series who

TABLE IV.—PERCENTAGE VOMITING IN EACH SERIES

	No atropine	Atropine 0·3 mg	Atropine 0·6 mg	Atropine 1·2 mg
No morphine	9·2*	15·1	8·8	0
Morphine 5·0 mg	21·7	19·7	14·0	8·5
Morphine 10·0 mg	51·7	27·5	23·2	14·8

*Saline 1·0 ml given as inert injection.

vomited and excludes those having nausea and retching only. Morphine given alone caused a marked increase in vomiting and this was more pronounced when a larger dose was used.

The action of atropine is again evident. Without morphine the incidence of vomiting was not reduced except with atropine 1·2 mg. With morphine 5·0 mg the reduction in the incidence of vomiting after atropine is apparent but is significant only with atropine 1·2 mg, but all doses of atropine significantly lessened the incidence of vomiting when morphine 10 mg was used. Comparing the incidence after the standard dose of atropine 0·6 mg and morphine 10 mg with that after morphine 10 mg alone, the beneficial effect of atropine is clearly evident; as is the significant increase in vomiting after morphine and atropine compared with atropine alone.

Discussion

Of interest is the finding that incidences of sickness varying from 3% to 67% were obtained when, as far as could be managed, the premedication was the only variable among the several series. It was unexpected that when no premedication was given the incidence of sickness should be as high as 22·4% after a minor and brief operative procedure under thiopentone alone.

The effect of morphine, when given alone, was almost entirely to increase the incidence of vomiting, while leaving virtually unchanged the incidence of nausea and retching only. Put in terms of the number of vomiting episodes per

100 patients the figure after saline was 12; after morphine 5·0 mg, 38; after morphine 10·0 mg, 106. This indicates the extent of the emetic effect of morphine in this study. Those patients sick after morphine frequently reported that movement of the body and the ingestion of fluids or food were precipitating factors. In addition the return of hunger was often delayed. The finding that the omission of morphine was followed by a lowering of the incidence of sickness agrees with the reports of Jaquenoud and Mercier, but the explanation is not clear. It is well established that the emetic and nauseant effects may last several hours (Wangeman and Hawk, 1942; Comroe and Dripps, 1948) so extending well into the post-operative period. The aggravating effects of movement, of recent food intake and of experimental vestibular stimulation in morphinized subjects have all been described (Comroe and Dripps, 1948; Steele, 1943; Rubin and Winston, 1950). The occurrence of duodenal contraction and concomitant nausea following morphine administration was studied in man by Ingelfinger and Moss (1942) but these workers did not think that the spasm actually caused nausea. In spite of many clinical and laboratory observations it is difficult to account for the high incidence of sickness, particularly vomiting, in fasting subjects at rest in bed following morphine 10 mg, a small operation and a small dose of thiopentone.

In the circumstances of this investigation, atropine was shown to have appreciable anti-emetic activity. In view of the statements of Goodman and Gilman (1955) and Reynolds and Randall (1957), and the report of Comroe and Dripps (1948) this was unexpected. Given alone the overall incidence of sickness was reduced by atropine to a greater extent with increase in the dose, but the incidence of nausea and retching only, was reduced to an equal extent by all doses. The effect of atropine on vomiting only was not so consistent. Thus with a dose of 0·3 mg an appreciable (though not significant) increase occurred. Atropine 0·6 mg had no effect, whereas twice this dose abolished vomiting. There thus appeared to be a dissociation between nausea and retching on one hand, and vomiting on the other. With morphine 5·0 mg, only the largest dose of atropine (1·2 mg) significantly lessened the incidence of nausea and retching, but when morphine 10 mg was used even the smallest dose of atropine significantly reduced the incidence of both vomiting and nausea and retching (Fig. 1).

If nausea and retching are regarded as lesser degrees of the disturbance which results in vomiting it might be expected that atropine in small doses would have counteracted these

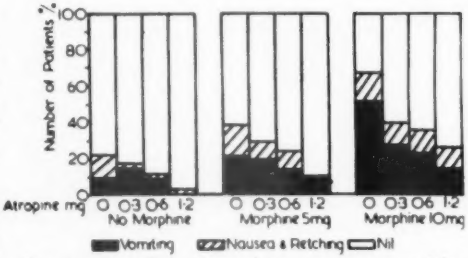

FIG. 1.—The effect of atropine upon nausea, retching and vomiting due to varying doses of morphine.

before reducing the frequency of vomiting. In the absence of morphine this occurred, but without any suggestion of an effect graded according to dose. With morphine 10·0 mg the effect against vomiting was marked, leaving the incidence of nausea and retching relatively unchanged.

The mechanism by which atropine antagonized the effect of morphine in premedication, and the sickness following operation and anæsthesia, is obscure. Atropine has not shown anti-emetic activity in animal experiments (Eggleston, 1917; Chen and Ensor, 1950; Boyd and Cassell, 1957). In humans it compared unfavourably with chloropromazine in modifying sickness due to apomorphine (Isaacs, 1956), but it is of value in motion sickness (Holling *et al.*, 1944).

Other Drugs Used in Place of Atropine

Morphine remains extensively used in pre-anæsthetic medication in spite of recommendations to the contrary (Beecher, 1955): but as atropine was found to minimize its emetic action it was decided to test the effects of other drugs, some having predominantly peripheral and others having marked central atropine-like effects. The results of this investigation are summarized in Tables V and VI.

TABLE V.—TEST DRUGS USED ALONE

	No. of patients in series	% nausea, retching and vomiting	% nausea and retching only	% vomiting
Saline 1·0 ml	76	22·4	13·2	9·2
Atropine 1·2 mg	113	11·5	2·7	8·8
Oxyphenonium 2·0 mg	38	13·2	5·3	7·9
Oxyphenonium 0·6 mg	52	13·5	3·9	9·6
Propantheline 15 mg	71	18·3	7·0	11·3
Hyoscine 0·6 mg	42	11·9	2·4	9·5
Phenglutarimide 5·0 mg	56	7·1	3·5	3·6
l-hyoscyamine 0·3 mg	84	10·7	3·6	7·1
Cyclizine 50 mg	77	5·2	2·6	2·6
Dimenhydrinate 50 mg	73	9·6	9·6	0
Halopyramine 20 mg	45	11·1	8·9	2·2
Perphenazine 5·0 mg	50	6·0	6·0	0
Tigan 100 mg	53	17·0	9·4	7·6
Pipamazine 10·0 mg	57	12·3	3·5	8·8

TABLE VI.—TEST DRUGS USED WITH MORPHINE 10·0 MG

	No. of patients in series	% nausea, retching and vomiting	% nausea and retching only	% vomiting
Morphine 10·0 mg* ..	87	66·7	14·9	51·7
Atropine 0·6 mg ..	108	35·2	12·0	23·2
Oxyphenonium 2·0 mg ..	43	44·2	20·9	23·3
Oxyphenonium 0·6 mg ..	30	53·3	26·6	26·7
Propantheline 15 mg ..	79	43·0	13·9	29·1
Hyoscine 0·6 mg ..	62	14·5	8·0	6·5
Phenglutarimide 5·0 mg	60	13·3	5·0	8·3
l-hyoscyamine 0·3 mg ..	73	20·6	4·2	16·4
Cyclizine 50 mg	78	14·1	3·8	10·3
Dimenhydrinate 50 mg	69	29·0	14·5	14·5
Halopyramine 20 mg ..	38	21·1	7·9	13·2
Perphenazine 5·0 mg ..	50	20·0	6·0	14·0
Tigan 100 mg	54	48·1	14·8	33·3
Pipamazine 10·0 mg ..	50	36·0	2·0	34·0

*The results following the use of morphine 10·0 mg alone are included for comparison.

Conclusion

Support is added to the movement to abandon the use of morphine before operation, but it remains to be seen whether this effect of morphine is of similar importance with other methods of anæsthesia and surgery. The use of hyoscine with morphine appears to be worth while although some anæsthetists object to the degree of sedation which it causes. Phenglutarimide which is less sedative and at least equally effective in reducing vomiting might well be considered: it is now known (Wyant and Haley, 1959) that it is an effective antisialogogue. Perphenazine which has quite a good sedative action was noted to have a marked effect in preventing vomiting in the absence of morphine and could perhaps be combined satisfactorily with atropine, thus enabling morphine to be dispensed with in pre-anæsthetic medication.

REFERENCES

BEECHER, H. K. (1955) *J. Amer. med. Ass.*, **157,** 242.

BELLVILLE, J. W., BROSS, I. D. J., and HOWLAND, W. S. (1959) *Anesthesiology*, **20,** 753.

BLUMFELD, J. (1909) *Med. Pr.*, **87,** 605.

BOULTON, T. B. (1955) *Anæsthesia*, **10,** 233.

BOYD, E. M., and CASSELL, W. A. (1957) *J. Pharmacol. exp. Ther.*, **119,** 390.

BURTLES, R., and PECKETT, B. W. (1957) *Brit. J. Anæsth.*, **29,** 114.

CHEN, G., and ENSOR, C. R. (1950) *J. Pharmacol. ex.p Ther.*, **98,** 245.

COMROE, J. H., and DRIPPS, R. D. (1948) *Surg. Gynec. Obstet.*, **87,** 221.

EGGLESTON, C. (1917) *J. Pharmacol. exp. Ther.*, **9,** 11.

GOODMAN, L. S., and GILMAN, A. (1955). The Pharmacological Basis of Therapeutics. 2nd ed. New York.

GORDH, T., and RYDIN, H. (1946) *Anesthesiology*, **7,** 526.

HOLLING, H. E., MCARDLE, B., and TROTTER, W. R. (1944) *Lancet*, i, 127.

INGELFINGER, F. J., and MOSS, R. E. (1942) *Amer. J. Physiol.*, **136,** 561.

ISAACS, B. (1956) *Clin. Sci.*, **15,** 177.

JAQUENOUD, P., and MERCIER, Y. (1951) *Anesth. Analg.*, **8,** 724.

——, —— (1952) *Anesth. Analg.*, **9,** 493.

MUSHIN, W. W., and WOOD, H. M. (1944) *Brit. med. J.*, i, 719.

PHILLIPS, O. C., NELSON, A. T., LYONS, W. B., GRAFF, T. D., and FRAZIER, T. M. (1958) *Anesth. Analg., Curr. Res.*, **37,** 341.

——, ——, ——, HARRIS, L. C., and FRAZIER, T. M. (1960) *Anesth. Analg., Curr. Res.*, **39,** 39.

REYNOLDS, A. K., and RANDALL, L. O. (1957) Morphine and Allied Drugs. Toronto.

RUBIN, A., and WINSTON, J. (1950) *J. clin. Invest.*, **29,** 1261.

STEELE, J. P. (1943) *Anesthesiology*, **4,** 430.

WANGEMAN, C. P., and HAWK, M. H. (1942) *Anesthesiology*, **3,** 24.

WYANT, G. M., and HALEY, F. C. (1959) *Anesthesiology*, **20,** 581.

DISCUSSION

Dr. Russell M. Davies (East Grinstead) said the four principal factors involved in post-operative vomiting were: (1) the premedication, (2) the anæsthetic itself, (3) the post-operative medication, and (4) the patient.

For almost one hundred years the main interest had revolved around the anæsthetic drugs. Ether increased vomiting. The addition of thiopentone decreased vomiting. The emphasis had so often been on *addition*. Later—when post-operative medication was the centre of interest—the addition, for example, of the phenothiazine compounds prevented or stopped post-operative vomiting. Dr. Riding's paper was one of relatively few which had dealt primarily with the effect of *pre-operative medication*, and one of the most telling points of his attack on the problem began with *subtraction*—not addition—the subtraction of morphine.

At East Grinstead in 1957 the post-operative vomiting rate was 37%—and in 1958, 28%—in unselected series of patients who had undergone plastic surgery. This reduction was largely due to the post-operative use of the phenothiazine compounds and cyclizine. In 1959 they had come to feel that the opiates were the most active offenders in causing post-operative vomiting. So they subtracted morphine and papaveretum and began to premedicate patients with promethazine—as a tranquillizer and anti-emetic; at the same time they gave first atropine and later hyoscine. At once the post-operative vomiting rate dropped from the 1958 level of 28% to 8%. This 1959 rate of 8% seemed too good to be true. It was! Post-operative restlessness increased tenfold—to the point of rebellion of the surgeons and Recovery Ward staff. This restlessness was thought to be due to the absence of an analgesic in the sequence—as anæsthesia was usually by relaxant, nitrous oxide and oxygen. So quite empirically pre-operative levorphanol was added to promethazine and hyoscine in doses of 0·5–2·0 mg. (For reasons irrelevant to this discussion it was not desired to use pethedine as an analgesic.) Forthwith the incidence of restlessness fell to its former and acceptable level.

Three further samples, of approximately 300 patients each, had been analysed. In *all* samples the percentage of patients vomiting *more* than three times had remained at approximately 1% of all patients. Any variation in vomiting incidence had been in the percentage of patients vomiting *less* than

three times. These samples showed quite clearly that the addition of any supplement to the anæsthetic sequence raised the post-operative vomiting rate. The groups which received ether, cyclopropane, halothane, and pethidine all showed a higher incidence of vomiting than did those who received relaxant, gas and oxygen. The sample in late 1959 showed 12% vomiting. The 1960 sample was 16%—so the rate was climbing again. But the relaxant nitrous oxide, oxygen technique was now less used than before, and the use of halothane had risen from 33% to 50% of cases. The use of other adjuvants had not significantly altered. It would appear that the rise in post-operative vomiting had closely corresponded to the increased use of halothane. Thus *addition* to the basic nitrous oxide and oxygen had brought an increased incidence of vomiting.

Some further points of interest had been indicated by these samples. It was confirmed that females vomit more than males. The likelihood of post-operative vomiting *decreased* with age and, in fact, out of nearly 1,000 patients only 2 men over 40 years of age vomited. Surgery in the zone of the airway appeared to have little effect on vomiting. Patients who were intubated seemed a little more likely to vomit than those *not* intubated.

The samples must only be regarded as rough indications, as they were not very large. Dr. Davies recommended more subtraction (particularly of the opiates) and less addition in drug sequences.

Dr. R. Burtles (London) agreed with Dr. Russell Davies that whilst drugs of the morphine and pethidine series increased post-operative vomiting, their omission created difficulties in post-operative restlessness. In addition, the analgesia provided by such drugs often formed an important part of certain anæsthetic techniques.

In contrast to Dr. Riding's beautifully controlled series, the overall figures for post-operative vomiting after halothane at the Middlesex Hospital were shown (Table I). The methods and criteria used

TABLE I.—POST-FLUOTHANE VOMITING

			Males		Females	
Total patients	327		125	(38%)	202	(62%)
All nauseated	31	(9.5%)	11	(35%)	20	(65%)
All who vomited	93	(28%)	26	(28%)	67	(72%)

	Combined		Males		Females	
Age and Sex	No.	% vomited	No.	% vomited	No.	% vomited
10–19	21	(48.5%)	9	(55%)	12	(42%)
20–39	101	(29.5%)	31	(23%)	70	(36%)
40 and over	204	(22%)	84	(13%)	120	(31%)

Duration of operation	No.	% nauseated	% vomited
Under 1 hour	228	10	20
Over 1 hour	99	12	50

		Vomiting	
Premedication	No.	Mild nausea	Mild	Moderate
Belladonna, pethidine, promethazine	167	8%	25%	2%
Belladonna, pethidine ..	142	11%	25%	5%
Belladonna	13	8%	25%	—
Others	5	20%	40%	—

were similar to those used in a previous publication (Burtles and Peckett, 1957, *Brit. J. Anæs.*, **29**, 114); no controls were made; it was felt that with so many factors being common to both series direct comparison was justifiable.

Of 327 patients in the series 28% had vomiting post-operatively; these figures suggested that in this respect halothane was not dissimilar to cyclopropane and trichlorethylene. 62% of the series were females, whereas 72% of those vomiting were of this sex. This increased liability to vomiting by females was shown to be present in each age group, and the incidence of post-operative vomiting was seen to decrease in both sexes with advancing years, thus confirming previous findings.

Also, it was shown that, in operations of more than one hour's duration, the vomiting rate rose, in this series from 20% to 50%, again confirming earlier findings. The exact significance of this was not easy to assess, but saturation with anæsthetic, severity of surgery and blood loss were likely to be factors.

In contrast to earlier findings, this series showed no alterations in vomiting rates when promethazine was used in the premedication. The reason for this was not known.

Dr. A. R. Hunter (Manchester) said that he had concentrated only on vomiting after recovery of consciousness, as this was the only vomiting which caused the patient discomfort.

He first studied post-operative vomiting in male Service patients during the 1939–45 war with a sharply defined group of patients undergoing a relatively limited number of operations. He had found that the incidence of post-operative vomiting was affected by premedication and that it was higher after barbiturate-atropine than after morphine-hyoscine or papaveretum-hyoscine. This difference was probably related to the post-operative use of morphine to control barbiturate restlessness. Appenpicectomy, either interval or emergency, carried a higher incidence of vomiting than did herniotomy, which was followed by as much vomiting as were extra-abdominal operations. A difference in the preparation of the cases in two different ward groups was of importance. Where castor oil was used for pre-operative purgation the incidence of vomiting was higher than where only an enema was employed. Increasing the duration of operation caused an increase in frequency of vomiting, which was also increased with the period of the patient's stay in hospital before operation. The substitution of nitrous oxide and oxygen and thiopentone given by the technique of Organe and Broad (1938) for volatile anæsthetics reduced the frequency of post-operative vomiting considerably. Later, in a hospital in which civilians and servicemen were treated in adjacent wards for the same conditions, the frequency of vomiting was less, though not significantly so, in the Service patient.

In civilian practice, Dr. Hunter found, as Dr. Riding did, that vomiting occurred more often in females. The substitution of spinal anæsthesia for general anæsthesia appeared to produce some reduction in the frequency in the vomiting of males but not in females. The use of thiopentone for induction before orthodox gas-oxygen-ether anæsthesia produced no improvement. The substitution of non-volatile supplements to nitrous oxide and oxygen produced a considerable reduction in the frequency of vomiting in civilian males but that among females remains relatively unchanged. More recently the

use of halothane as a supplement to nitrous oxide and oxygen had produced a small, though as yet not statistically significant reduction in the overall incidence of vomiting among women, but within the single group of breast operations it was statistically significant.

Finally, the administration of perphenazine (Fentazin) intramuscularly at the end of operation in doses of 0·5 mg per stone up to 5 mg had produced a significant reduction in the vomiting incidence in patients under nitrous oxide and oxygen and halothane, in a small though fully controlled series of female patients undergoing comparable operations.

REFERENCE

ORGANE, G., and BROAD, R. J. B. (1938) *Lancet*, ii, 1170.

Dr. M. D. Vickers (London) questioned the validity of dividing up the results into nausea and retching, on the one hand, and vomiting, on the other. Nausea might be not only centrally produced, but entirely the result of emotion, and thus not affected by some of the drugs under discussion. It was also wholly subjective, and the term nausea might not mean the same to all patients, e.g. it might be equated with dizziness. Retching might or might not result in vomiting, depending on whether or not there was anything in the stomach. It would seem more valid, therefore to rearrange the results as "nausea", and "retching and vomiting". Different conclusions might then be drawn.

As to the anti-emetic properties of atropine, might it not be that with the delayed emptying of the stomach after the morphine, aided by the emotional effects of the impending operation, the increasing dosage of atropine diminished the amount of swallowed saliva, and thus deprived the patient of anything to bring up post-operatively?

It was also suggested that the speaker's patients, being all women who had recently had a miscarriage, were likely to have been highly affected emotionally, thus explaining his apparently high incidence of these complications.

Dr. D. D. C. Howat (London) said that, in the course of an investigation into the effects of two phenothiazine derivatives on post-operative vomiting, he had found, like Dr. Russell Davies, that vomiting occurred two or three times more commonly in women than in men. There had also been a suggestion that the use of pethidine to control the tachypnœa caused by trichlorethylene or halothane was followed by a higher incidence of post-operative vomiting than when pethidine or a halogen derivative was used separately.

Dr. E. K. Brownrigg (Basingstoke) said that suggestion was an aspect of the subject which had not so far been mentioned. He illustrated this point by describing 2 cases. The first was a girl of 14 years whose limbs were being fixed by post-hypnotic suggestion for the transfer of a tube pedicle from abdomen to foot. Suggestions of a feeling of post-operative well-being were made under deep hypnosis. The second was a woman of 25 years to whom similar suggestions were made after the injection of 75 mg of thiopentone.

Both patients had previously vomited after every anæsthetic. The second patient even vomited after every dental extraction under nitrous oxide. Neither patient vomited after anæsthesia preceded by suggestion.

Dr. H. B. C. Sandiford (Portsmouth) said he had kept figures relating to vomiting following anæsthesia for ophthalmic surgery. Two points only had emerged: (1) When traction was applied to extrinsic ocular muscles, as in operations for strabismus, the vomiting rate could be high. (2) The incidence of vomiting varied with different anæsthetists.

Dr. J. E. Riding, in reply, said that he was interested to hear that Dr. Davies had noted a reduction in the incidence of sickness following the omission of pre-operative opiate. His own impression had been that promethazine, and also pentobarbitone, given without analgesics before operation was associated with increased post-operative restlessness following relaxant, nitrous oxide and oxygen.

Once again the increased liability of females to vomit was shown by Dr. Burtles' results. This seemed to be one of the few influencing factors about which there was no dispute.

Dr. Hunter's findings of, and explanation for, a higher incidence after barbiturate and atropine premedication were reminiscent of Smith's results (1934, *Brit. J. Anæs.*, **11**, 132). Dr. Riding noted Dr. Hunter's use of perphenazine at the end of operation, but felt that it should be reserved for use in established post-operative vomiting since not all patients vomited, and drugs of this type might have unpleasant side-effects, and were not 100% effective.

In reply to Dr. Vickers, Dr. Riding accepted that the results might be dealt with differently. As he had pointed out earlier, there was little agreement on how best to deal with these. Probably the simple separation of those who were sick from those who were not, according to the chosen criteria of post-operative vomiting, was most valuable. Nausea was certainly a psychic experience and difficult to measure. Whether retching should be grouped with vomiting was a matter of opinion. Vomiting was separated intentionally because of its objective nature. Dr. Riding doubted that essentially different conclusions would have been reached by the suggested regrouping of results. He did not agree with the explanation for the anti-emetic activity of atropine. Both oxyphenonium and propantheline, having powerful peripheral atropine-like actions, had proved less effective than atropine in this investigation when used with or without morphine. Cyclizine and dimenhydrinate on the other hand, which showed much weaker anti-salivary activity, had strong anti-emetic effects with or without morphine.

Regarding the emotional state of the patients, this seemed a very unlikely explanation in view of the wide range of incidences observed. Not all patients were disturbed by the loss of a pregnancy. In addition those patients receiving atropine 1·2 mg had the lowest incidence of sickness and at the same time were excited and restless pre-operatively. A comparable series of non-pregnant patients having minor gynæcological operations showed an incidence of 57% compared with 35% in the present investigation, following in both cases premedication with morphine 10 mg and atropine 0·6 mg.

Meeting
April 1, 1960

Dehydration Therapy in Cerebral Hypoxia [*Abridged*]

By D. H. P. Cope, M.B., F.F.A.R.C.S.
London

The clinical consequences of cerebral anoxia are well known and the residual effects vary greatly in their presentation and their eventual outcome (Allison and Bedford, 1956).

Advances in anæsthesia have not, unfortunately, reduced the number of patients who may suffer a severe anoxic or hypoxic episode. On the contrary they have enabled many more patients to become eligible for this doubtful privilege. Patients who twenty years ago would have been considered unfit for anæsthesia and operation are now able to benefit from surgical treatment. More heroic surgical procedures have been made possible; lung and heart surgery are now commonplace. In addition resuscitation of the moribund is more energetic, and the increase nowadays of poliomyelitis and acute polyneuritis all contribute to the number of patients at risk.

In spite of every care taken for their prevention, anoxic accidents still occur, therefore, and once adequate oxygenation has been resumed a regimen of active treatment should be instituted.

Dehydration therapy is not a new form of treatment, but it is still not employed nearly as often as it should be. Ten years ago Lucas (1950) described a case of cardiac arrest treated by dehydration with 50% glucose. Other treated cases have been reported from time to time (Seldon *et al.*, 1949; Cole, 1951; Sadove *et al.*, 1953) but almost without exception they refer to patients whose cerebral anoxia was caused by cardiac arrest. Argent and Cope (1956) stressed that similar pathology and equally serious sequelæ may occur in patients who have had hypoxic episodes far short of cardiac arrest, and that dehydration therapy should also be applied to them. Raison (1957) confirmed this opinion.

Pathology

The rationale of dehydration by hypertonic solutions may best be understood by reference to the changes that occur in the brain when it is subjected to anoxia or severe hypoxia (Fig. 1). Damage to the brain cells is determined chiefly by the degree and duration of the hypoxic period and though some cerebral cells may be completely destroyed, others are not so severely affected and, under suitable conditions, their damage is reversible. We agree with the theory that the main factor preventing recovery of these cells is cerebral œdema, occurring as a result of simultaneous hypoxic damage to the cerebral blood vessels. Capillary rupture and increased permeability permit crystalloids and plasma proteins to escape from the vessels into the intercellular spaces drawing water out with them. This œdema fluid acts as a physical barrier and interferes with the passage of oxygen across the intercellular spaces to the reversibly damaged cells; their hypoxic state is increased and irreversible changes may now set in.

In addition, cerebral œdema sets up a vicious circle of raised intracranial pressure, venous obstruction, and further œdema. Respiratory depression results and hypoxia increases. McDowall (1952), furthermore, has shown that during anoxia intracellular œdema occurs due to a disturbance of the electrolytic balance; sodium chloride passes into the cell leading to water retention which further obstructs the passage of oxygen in the cell. All these mechanisms prejudice the chances of cellular recovery and the patient's future welfare.

Causes

We believe that this sequence of events occurs much more commonly and with less severe hypoxia than is generally realized (Argent and Cope, 1956). We have treated many cases of hypoxia due to a wide variety of causes. These have included carbon monoxide poisoning, respiratory obstruction due to inhalation of

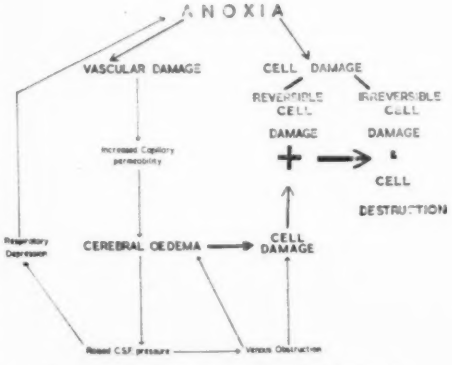

FIG. 1.—Vicious circle of cerebral hypoxia.

vomit or carcinoma of the larynx, profound hypotension from a variety of causes, prolonged hypoventilation from poliomyelitis or difficult thoracic operations as well as cardiac arrest and prolonged circulatory occlusion during hypothermia. Hypoxia may occur in any ward of a general hospital and it behoves us all to be alert to its occurrence, for if the pathology be as described then the earlier dehydration therapy is instituted the greater will be the chances of maximal recovery.

Clinical Signs of Cerebral Hypoxia

Usually a history of an anoxic or hypoxic episode is obtained but this may not be clear cut. It is important to realize that although complete recovery of consciousness may occur, the patient may yet relapse into coma some hours later. The depth of coma varies with the extent of the cerebral damage and the duration and the severity of the hypoxia. Respiration is stertorous, or jerky and gasping; a tracheal tug is frequently present.

Hyperpyrexia is usual but not necessarily present initially, there is sweating of the face and neck. Pupils are dilated and commonly equal in size, there may be a coarse nystagmus and the eyes may be open and staring. Fits, restlessness, twitching of the limbs, rigidity and choreoathetosis may all occur. The terminal picture is characterized by deepening coma, general flaccidity, Cheyne-Stokes respiration, and increasing pulse-rate and pyrexia.

Post-operatively cerebral hypoxia must be distinguished from conditions such as CO_2 retention, and partial curarization; it may, however, be superimposed on either of these states.

Treatment

Once a diagnosis of cerebral hypoxia has been made and adequate oxygenation ensured, dehydration treatment should be started without delay. The hypertonic solutions that we use are 50% sucrose, and more recently, 30% urea in invert sugar. We prefer these substances because they are neither metabolized nor stored in the body, thus a secondary rebound of intracranial pressure is avoided; they are entirely excreted in the urine, effecting a marked and early diuresis which is beneficial in these cases.

50 ml of 50% sucrose are given intravenously and any change in the level of consciousness is noted over the next quarter-hour. Two further injections of 50 ml are given at half-hourly intervals and the position reassessed.

Three states may now be apparent: (1) If there has been no obvious benefit from the injection of 150–200 ml of 50% sucrose it is probable that the initial hypoxia was very severe, irreversible cell damage extensive and recovery is most unlikely to occur. (2) Alternatively the patient may have completely recovered from his coma and show no evidence of any residual damage. Care should be taken that these quick recovery cases do not relapse back into a confused or lightly comatose state within the next three hours; if deterioration occurs a further 50 ml of 50% sucrose will effect a permanent recovery. (3) Patients whose coma and physical signs have improved considerably but who are not yet properly conscious are put on to a 50% sucrose drip run at 1 ml per minute, or preferably a 30% urea drip in a dose of 1 g/kg of body weight and run in at 4 ml per minute. In this group the outcome is extremely difficult to forecast. If coma appears likely to last more than a few hours attention must also be paid to the maintenance of blood pressure and to the state of the bladder; a Ryle's tube must be passed to prevent acute dilatation of the stomach. A head-up position is ideal to encourage cerebral decongestion, though care should be taken that vasomotor collapse does not occur. Antibiotics, physiotherapy and perhaps tracheostomy will be necessary to prevent chest complications. Hypothermia must be seriously considered. Sadove (1960) thinks that insufficient use is made of EEGs for assessing the trend and prognosis of these cases. He considers that early return of the faster 12–14/sec waves is a good sign.

The recent reintroduction of 30% urea is an advance over 50% sucrose; not only has it about 3·5 times the osmotic power, volume for volume, but its effects are longer lasting, so that for this last group of patients it would be ideal. At the moment difficulties with sterilization and presentation make it very expensive and not universally available. If neither urea nor sucrose is at hand, quadruple strength plasma or 10% dextran may be used with effect, though there is a risk of serum jaundice with the former, and both have the disadvantage of not being excreted.

It is possible in some cases that evidence of a clear-cut hypoxic episode is lacking, e.g. after chronic under-ventilation during a thoracotomy, or where two hypoxic elements are operating simultaneously, as when severe bronchospasm or inhalation of gastric contents occurs in a shocked or anæmic patient. Here the damaging effects on the brain summate, though the hypoxia caused by each factor alone would not be expected to raise any alarm. In such cases of coma, where there is only some presumptive evidence of possible hypoxic damage, we do not hesitate to administer 50–100 ml of 50% sucrose, for if the unconsciousness be due to cerebral œdema

immediate improvement will occur and enable the correct treatment to be employed.

There is no good evidence to show that this dose would harm any patient (unless there be a cerebral hæmorrhage), even if the coma were not hypoxic in origin.

Some of the foregoing points are illustrated by 4 recent cases.

Case I.—Hypoxic cerebral damage due to circulatory occlusion under hypothermia.

This case shows a mild degree of cerebral hypoxia and a late relapse.

A 26-year-old male with congenital aortic stenosis.

2 p.m.: Aortic valvotomy under general anæsthetic and surface hypothermia. Operation was expected to be very straightforward and the temperature was not brought down low enough for the unforeseen difficulties that arose. In addition the suture line leaked and further occlusion had to be effected. The cerebral circulation was occluded for 7 min 15 sec at nasopharyngeal temperature 32·8°C and for 2 min 30 sec at nasopharyngeal temperature 33·1°C.

5 p.m.: Rewarmed and back in bed.

6 p.m.: Still unconscious, very restless.

8 p.m.: Still unconscious, extremely restless. No other evidence of hypoxic damage.

50 ml 50% sucrose I.V.

8.15 p.m.: Much quieter, woke up and talked coherently.

9.45 p.m.: Restlessness increasing again, lapsing into coma. *75 ml 50% sucrose.* Woke up at once and complained of pain in the wound. Uneventful immediate post-operative course with no residual mental or neurological abnormality.

Case II.—Hypoxic cerebral damage due to chronic underventilation.

Patient had no obvious hypoxic episode, but showed progressive signs of cerebral damage post-operatively.

A 53-year-old obese female had a two and a half-hour thoracotomy for repair of hiatus hernia.

1.30 p.m. (immediately after operation): Congested appearance and slight cyanosis; sweating and grunting respiration. Unrousable.

2 p.m.: No improvement after twenty minutes' vigorous hyperventilation. Plantar reflex upgoing.

3.30 p.m.: As above but pupils now dilated.

4.45 p.m.: As above but respiration now jerky, irregular and shallow.

5.45 p.m.: Decerebrate behaviour; sham rage reaction; no eyelid reflex; pupils dilated and unreactive to light; limbs now spastic.

40 ml 50% sucrose I.V.

6.30 p.m.: Pupils smaller, react to light; eyelid reflex present. Still unconscious; plantar response equivocal.

7 p.m.: *40 ml 50% sucrose I.V.*

7.30 p.m.: Just rousable; not orientated; lying quietly; normal limb tone and posture. Respiration normal pattern. Over the next two hours continued improvement but a bit confused. No neurological findings apart from this. Patient had amnesia of first post-operative day but no other evidence of residual hypoxic damage.

Case III.—Hypoxic cerebral damage due to carbon monoxide poisoning.

Case showing good recovery in spite of long delay in starting dehydration.

7.30 a.m.: A 55-year-old man, found unconscious having inhaled coal gas from a tube attached to a gas jet. Dragged to another room. Nine hours later still in coma so a doctor was called.

5.30 p.m.: Admitted to hospital; deeply comatose, with some respiratory obstruction. Guedel airway inserted; oxygen given. No response to painful stimuli; pupils central and widely dilated. Blood pressure and pulse-rate normal.

6 p.m.: *60 ml 50% sucrose I.V.* No obvious benefit.

6.10 p.m.; *100 ml 50% sucrose I.V.* Patient responded to painful stimuli; pupils smaller and eyeballs rolling.

6.20 p.m.: Very restless; a further *60 ml 50% sucrose* necessitated restraint to keep him in bed.

8 p.m.: Responded to name and fairly rational although tended to fall asleep if not spoken to.

10 p.m.: Fully awake; no residual neurological findings.

Case IV.—Hypoxic cerebral damage due to induced hypotension.

Case shows late onset of severe cerebral hypoxia.

2 p.m.: A 71-year-old male had a laryngectomy performed and for a variety of reasons controlled hypotension was deemed essential. A Trophenium drip was set up but due to sudden relaxation of venospasm a large overdose had run in before this was appreciated. Patient became pulseless and developed Cheynes-Stokes respiration before resuscitative measures had taken effect.

6.30 p.m.: End of operation. Responded to name; moved limbs; reflexes normal and no evidence of hypoxic damage.

8.30 p.m.: Awake and no evidence of hypoxic cerebral damage.

11 p.m.: Found deeply comatose. Right pupil widely dilated; no response to pain; right plantar upgoing; sweating ++; temperature 99·8°F; respiration jerky, 40 per minute.

60 ml 50% sucrose. Coma lighter; pupils equal and small; responded to pain; made inco-ordinated limb movements.

11.30 p.m.: *30 ml 50% sucrose.* Consciousness regained; responded to name and commands. Restless.

Post-operative amnesia of thirty hours; otherwise no abnormal neurological signs or sequelæ.

These cases might have recovered without dehydration therapy, but I would not be prepared to say when, or with what residual lesions. It was to try and clarify this point that we carried out experiments in dogs in the Institute of Clinical Research, Middlesex Hospital (Argent, 1960; Buxton, 1960).

None of the patients quoted above had a cardiac arrest; and were not even, except Case IV,

in imminent danger of an arrest, yet all had evidence of severe cerebral damage. The fact that the coma was in one case delayed and in the others progressive, strongly suggests that cell damage at the time of the hypoxic episode is only part of the story. Interference with the recovery of reversibly damaged cells by cerebral œdema almost certainly causes these secondary and later effects. It is not generally appreciated that hypertonic solutions have such a dramatic effect in these cases of cerebral hypoxia; indeed it is just these cases where the initial irreversible damage is probably slight that should show maximal benefit and complete recovery provided the vicious circle of cerebral œdema is broken.

REFERENCES

ALLISON, R. S., and BEDFORD, P. D. (1956) *Proc. R. Soc. Med.*, **49**, 609.
ARGENT, D. E. (1960) *Proc. R. Soc. Med.*, **53**, 681.
—— and COPE, D. H. P. (1956) *Brit. med. J.*, i, 593.
BUXTON, P. H. (1960) *Proc. R. Soc. Med.*, **53**, 683.
COLE, F. (1951) *J. Amer. med. Ass.*, **147**, 1563.
LUCAS, B. G. B. (1950) *Proc. R. Soc. Med.*, **43**, 606.
MCDOWALL, R. J. S. (1952) *Proc. R. Soc. Med.*, **45**, 747.
RAISON, J. C. A. (1957) *Lancet*, ii, 984.
SADOVE, M. S. (1960) Personal communication.
——, WYANT, G. M., and GITTELSON, L. A. (1953) *Brit. med. J.*, ii, 255.
SELDON, T. H., FAULCONER, A., and COURTIN, R. F. (1949) *Proc. Mayo Clin.*, **24**, 370.

Experimental Hypoxia in Dogs [*Abridged*]

By D. E. ARGENT, F.F.A.R.C.S., D.A.

Portsmouth

THE experimental evidence necessary to support our thesis and to confirm the success we have had in the treatment of cerebral hypoxia clinically has been extremely difficult to obtain. The difficulties are obvious. In man, with his highly developed brain, it is relatively easy to show minor changes in personality or major damage to the central nervous system (Bedford, 1955) whilst similar changes in animals are difficult to detect.

Yant *et al.* (1934) showed that cerebral œdema occurred in dogs killed after breathing an oxygen-deficient mixture and that the appearance of the brain was similar to that found in carbon-monoxide poisoning. There was severe peri-vascular and perineuronal œdema involving the cortex, the corpus striatum, and the dorsal nucleus of the vagus. In slow carbon-monoxide poisoning the œdema was so severe that the specimen had the appearance of an artificially injected preparation.

Chornyak (1938) was able to show, in monkeys given pneumonia experimentally, that there was a direct relationship between the amount of brain damage and the amount of lung involvement. He was also able to study patients who had died of bronchopneumonia and there too showed a similar correlation.

In our experiments, dogs were anæsthetized with 2·5% thiopentone sodium in a dosage of 12 mg/kg body weight. They were intubated under topical anæsthesia with 4% lignocaine and anæsthesia was maintained with 90% nitrous oxide and 10% oxygen. The femoral artery was cannulated so that an accurate recording of the blood pressure could be obtained and the respiratory pattern was also recorded. The animals were subjected to six successive attacks of anoxia at intervals of ten minutes by merely cutting off the oxygen supply. This technique is a variation on that described by Dessoille (1932).

The response to anoxia was at first a period of hyperventilation followed by respiratory arrest with a subsequent fall in blood pressure as circulatory failure occurred. When the fall of pressure reached 50 mm Hg, artificial ventilation with pure oxygen was instituted and recovery ensued. The characteristic feature of this recovery was the large rise in blood pressure, often to 300 mm Hg which took place before normal respiration returned. After 10 minutes when the animal had settled to normal the procedure was repeated, and after six such episodes the preparation was complete. The recovery of the animal from each episode became progressively less, and indeed 30% of our animals perished either during the preparation or at some later date, a fact which led us to believe that the degree of hypoxia was severe.

The cannula was removed and the dogs breathed pure air from then on. They were either left untreated or were given 50% sucrose intravenously and all animals were killed on the fourteenth day for post-mortem examination.

In order to assess the benefits of treatment a system of "points" scoring according to a predetermined scale was evolved, as follows:

Score 0. Comatose, unresponsive to call or stimuli.
1. Consciousness regained.
2. Consciousness and standing but ataxic.
3. Conscious and standing but not ataxic.
4. Appearing normal but anorexic, diarrhœa or cough.
5. Appearing normal and well.

The scores were recorded at half, two, six and twenty-four hours and at two, seven and fourteen days after the end of the preparation. The maximum possible points for each was therefore 35.

The majority of the treated animals had a higher score than the untreated (Fig. 1) when all the scores were totalled, indicating a more rapid return to normal.

animals were comatose and therefore scored 0. At half an hour a slight difference may be seen between the treated and the untreated groups, but the greatest difference occurs between the six- and twenty-four-hour periods, presumably when the œdema was exerting its maximal effect in the untreated cases.

It is a little disappointing that we have not been

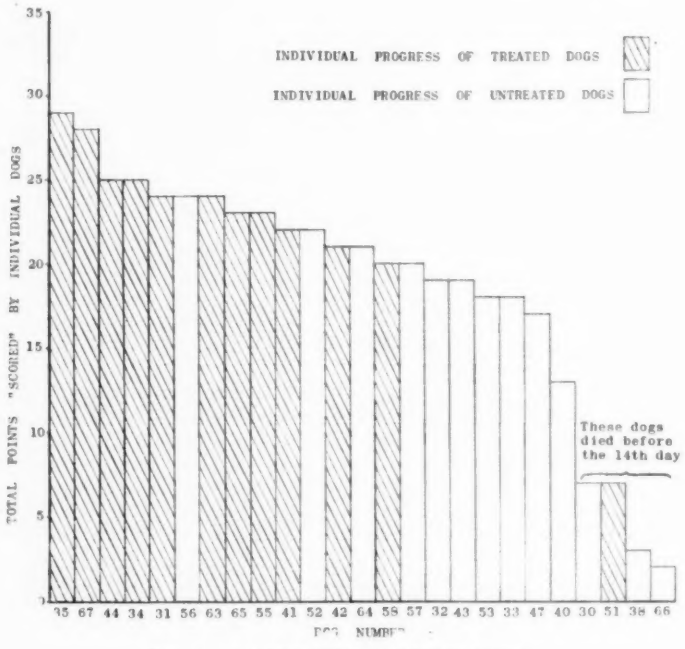

FIG. 1.—Individual progress following anoxia.

If these scores are now plotted by taking the mean score for each group at each assessment time a most interesting pattern arises (Fig. 2). At the conclusion of the preparation all the

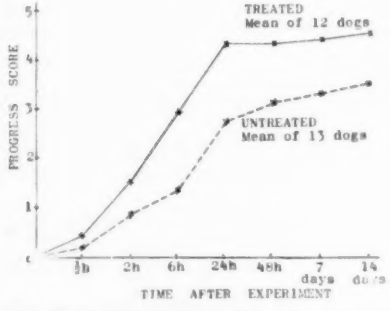

FIG. 2.—Average progress following anoxia.

able to demonstrate a wide variety of post-anoxic sequelæ similar to that seen in man, but I am sure that this is due to the relatively low position that dogs hold in the phylogenetic scale; had we been able to use monkeys we should have demonstrated a wider differential between the treated and the untreated groups. Nevertheless I feel that the results substantiate our belief in the early treatment of cerebral hypoxia by dehydration therapy, especially with 50% sucrose in the first instance, in order that the appalling results of irreversible cerebral damage may be avoided.

REFERENCES

BEDFORD, P. D. (1955) *Lancet*, ii, 259.
CHORNYAK, J. (1938) *Univ. Hosp. Bull. Mich.*, **4**, 77.
DESSOILLE, H. (1932) Les Troubles Nerveux dus aux Asphyxies Aiguës, Paris.
YANT, W. P., CHORNYAK, J., SCHRENK, H. H., PATTY, F. A., and SAYERS, R. R. (1934) *Publ. Hlth Bull., Wash.*, No. 211.

Neuropathological Findings in Experimental Hypoxia [*Abridged*]

By Peter H. Buxton, M.D., M.R.C.P.
London

The object of this study was to investigate the mechanisms of post-anoxic cerebral damage in dogs and to compare the neuropathological changes in the treated and untreated animals. It was hoped in this way to substantiate the hypothesis that late anoxic cerebral damage was due in part at least to œdema, particularly in the white matter, which might respond to dehydration therapy.

In our early experiments attempts were made to demonstrate the acute phase of œdema by examining the brains of animals sacrificed two hours after a severe anoxic episode. Thus brains were perfused immediately after death with 0·5% trypan blue. Broman (1950, ***Acta psychiat., Kbh.*, 25,** 19) has shown that trypan blue given intravenously does not transgress the blood-brain barrier unless there has been damage to the capillary walls; this effect has been found to persist up to two hours after death. In our experiments the existence of capillary damage was confirmed, in that staining was usually demonstrated in areas where there was later proved to be obvious histological change. However, we found that this method lacked sufficient precision. In addition, in these acute phase experiments, direct estimations of fluid and electrolyte content of grey and white matter were made by removing a core of brain tissue through a trephine hole immediately after death. While the results tended to confirm the presence of œdema, they were far from clear cut, probably owing to the small amount of tissue available.

The main series of experiments was designed to investigate the neuropathological changes fourteen days after the anoxic insult; by this time the clinical condition was static and histological changes could be expected in the brain. The results presented were obtained from examination of brains removed within two hours of death and fixed in 10% formol saline for a minimum period of ten days. They were then sectioned coronally at centimetre intervals. No abnormalities were seen macroscopically other than slight or moderate congestion, except in animals 30 and 51 where there was cortical softening: these 2 cases showed the most severe microscopical damage. Paraffin blocks and frozen sections were then prepared and selected sections were stained by conventional methods.

The most frequently affected sites of maximal damage[1] were the central grey matter (thalamus, globus pallidus, corpus luysi and substantia nigra) and the cerebral cortex, the hippocampus being particularly affected, though severe cortical damage, when it occurred, tended to be widespread and included the calcarine cortex. In the cerebellar cortex, Purkinje cell loss was often found and the dentate and inferior olivary nuclei not infrequently showed damage. In assessing the type and severity of histological changes such factors as frank necrosis, nerve cell destruction, axon and myelin sheath damage, glial reaction and capillary proliferation were considered. A system of grading was used in which 4 pluses signified the most severe lesions. The histological assessment was made quite independently of the "clinical" assessment. (Table I.)

[1]Slides were shown to illustrate these changes.

Table I.—Extent of Damage

Dog	Cortex	Cornu ammonis	White matter	Thalamus striatum	Globus pallidus, corpus luysi	Purkinje	Dentate	Olive	Survival	"Clinical" assessment of damage
32	—	+	+ +	+ + +	+ + +	+ +	+	+ +	•	+ + + +
33	+	+ +	+ +	+ + +	+ +	+ + +	+ +		•	+ +
40	—	—	+ +	+ +	+	—	—		•	+ + +
43	+ +	+ +	+ + +	+ + + +	+ + + +	+ + +	+ +	+	•	+
47	+	+	+ +	+ +	+	+	+ +	—	•	+ +
52	+		+ + +	+ + +	+ + +	+ +	+	+ +	•	+
53	+	+	+	+ +	+ +	+ +	+	+	•	+ +
56	—	+	+	+	+	+	+	—	•	—
57	+	+	+	+	+	+ +	+	—	•	+
64	+ +	+	—	+	—	—	—	—	•	+
30	+ + + +	+ + +	+ +	+ + +	+ +	+ + +	+		68 hours	+ + + +
38	+ +	+ +	—	+ +	+	+	+		36 hours	+ + + +
51	+ + + +		+ + +	+ + +	+ +	+ +	+ +		48 hours	+ + + +
31	—		+ +	+ +	+	+ +	+		•	—
34	—	+	—	+	—	+	—	+	•	—
35	—	+	+	+	+ + +	—	—	+	•	—
41	+	+ +	+ +	+ + +	+ + + +	+	+	+	•	+
42	—	+ +	+ + +	+ +	+ +	+ +	+		•	+
44	—	—	—	+	—	—	—	—	•	—
55	—		—	+ +	+ +	+ +	+	—	•	—
58	+	+ +	+	+ +	+ +	+	+	+	•	+
63	—	—	+	+	+	—	+	—	•	—
65	—	+	—	—	—	—	—	—	•	—
67	+	+ +	+	+	+	+ +	+	+	•	—

[1] These animals were sacrificed after fourteen days.

The column "clinical assessment" is derived from the "points system" chart shown by Dr. Argent (Fig. 1, p. 682), in which the most severely affected animals were given low scores whereas in Table I these have been allotted pluses. The scoring has been inverted in this way to facilitate comparison within Table I.

The upper group of cases received no treatment after their anoxia: the lower group had dehydration therapy.

The close agreement between the clinical assessment and the pathological findings in both groups is demonstrated. The susceptibility of the central grey matter and the cerebellar Purkinje cells to anoxia is also shown. Of particular interest are the gross changes occurring within forty-eight hours in specimens 38 and 51. The paucity of clinical signs in some cases in which marked damage to the central grey matter can be seen is also noteworthy.

The most pronounced differences between the treated and untreated groups are in the degree of cortical and white matter damage; these correspond reasonably well with the "clinical" assessment. There is also less severe damage in the central grey matter in the treated group. If the three animals 30, 38 and 51—all of which showed very severe anoxic damage and lived less than three days—are removed from the series the differences between the treated and untreated groups are even more apparent. Nevertheless it is somewhat disappointing that no more clear-cut differences emerged between the two groups, particularly in the white matter which, due to local physical factors, is well known to be more affected by œdema than is grey matter. Changes in the white matter, however, such as focal necrosis, patchy myelin loss and glial reaction are in general more prominent in the untreated group, and in the treated groups represent those changes which had not been reversed by therapy. Despite the microglial activity and astrocytic proliferation in these cases, only minor increase in glial fibres can be demonstrated. This may well be due to the relatively short survival time after the anoxic episode; Scholz *et al.* (1959),[1] quoting Muller, give periods of nine to sixteen days for development of first glial fibres after injury due to infarct. More marked differential gliosis between the two groups would undoubtedly have developed if the animals had been allowed to survive for longer after their anoxia. In four to six weeks after damage glial fibres should be visible to the naked eye in a Holzer section.

[1]Scholz, W., Boellaard, J. W., and Hager, H. (1959) *Technical Report*. Contract No. AF 61 (514) - 945. U.S.A.F.

The cortical changes in the two groups, though different in degree, show no qualitative difference and the same is true of the central grey matter.

This work was carried out at the Institute of Clinical Research, Middlesex Hospital, and at the Maida Vale Hospital for Nervous Diseases.

DISCUSSION

Dr. J. G. Bourne (London and Salisbury) asked why the method of Kabat and Dennis (1938, *Proc. soc. exp. Biol., N.Y.*, **38**, 864) had not been used in the dog experiments. This was a precision method that allowed cerebral anoxia to be accurately controlled and gave predictable results. It might have facilitated the detection of histological differences between treated and untreated animals.

He asked also whether histological examinations had been made of the brains of dogs that had had severe anoxic sequels and then made a complete clinical recovery. In human cases, eventual clinical recovery often seemed to be accepted, even by neurologists, as evidence that the brain had escaped damage. But he doubted whether this was a safe assumption and felt that, in such cases, the brain might well be found, if it were examined under the microscope, to have suffered permanent neuronal damage.

Dr. Sheila Anderson (London) asked Dr. Cope if he had any experience of the long-term use of urea in repeated dosage to reduce intracranial tension. If so, she would like to know of any complications which could have been caused by the urea.

Dr. J. F. Nunn (London) asked if the scatter of the results would be reduced at all by using an inbred strain of animals, such as Wistar rats, and if intravenous sucrose could cause damage to the renal tubules.

Dr. D. H. P. Cope, in reply to questions, said that he had not seen any toxic reactions from the use of 50% sucrose. Renal damage had been reported by Anderson and Bethea (1940, *J. Amer. med. Ass.*, **114**, 1983), but as their 6 cases had previous renal damage from hypertensive encephalopathy and had been given very large doses of sucrose their findings could be disregarded in the type of case dealt with here. Lindberg *et al.* (1939, *Arch. intern. Med.*, **63**, 907) had reported normal urea clearance and unimpaired renal function in 15 normal patients following 200 ml 50% sucrose. Local thrombophlebitis was alleged to occur but he had had no trouble in this respect.

His experience with 30% urea was still small and it was difficult to say what total amount should be given. The calculated dose of 1 g/kg was infused over a period of about one hour; if further dehydration seemed indicated half this quantity could be given over the next four hours. He would say that if this total dose had not resulted in marked improvement further dehydration attempts were unwarranted and the situation indicated severe irreversible cerebral damage.

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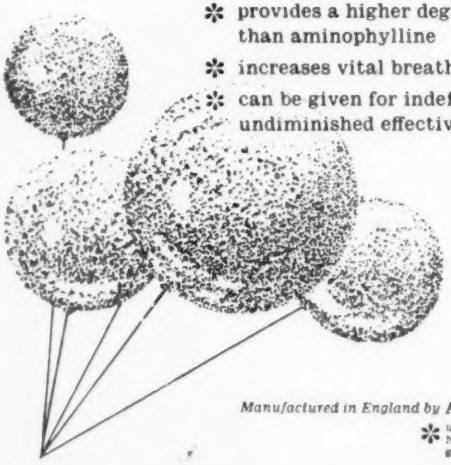

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Section of Urology

President—D. S. POOLE-WILSON, M.Ch., F.R.C.S.

Meeting
February 25, 1960

The Pathology of Fibrotic Lesions

By R. C. B. PUGH, M.D.

London

IDIOPATHIC retroperitoneal fibrosis and Peyronie's disease are two manifestations of the many known types of disordered growth of collagen that occur in generalized or localized form in different parts of the body. The pathological features of these two conditions will be presented, illustrated with details of a case of each type, and the two diseases will then be considered briefly in the wider context of the known forms of collagen disease.

IDIOPATHIC RETROPERITONEAL FIBROSIS

This condition, which has been recognized only recently (Pérard and Orsini, 1937; Ormond, 1948), affects men three times as frequently as women, has its maximum incidence in the fourth decade and is characterized by the development of a plaque of tough fibrous tissue in the retroperitoneal tissues of the posterior abdominal wall, producing secondary changes in the various structures normally found there. For reasons not yet understood the smaller lesions usually commence between the pelvic brim and the aortic bifurcation, but in a fully developed case there is involvement of a roughly rectangular area bounded above by the renal hila and laterally by a line about 1 cm lateral to the ureters. Occasionally one or other kidney is involved and its perinephric fat is considerably thickened; in one of Raper's (1956) cases the plaque extended above the diaphragm and caused obstructive jaundice.

Many authors believe that the size and shape of the fully developed lesion are determined by the limits of the renal fascial compartment of Gerota and, indeed, some refer to the condition as perirenal or Gerota's fasciitis (Hutch *et al.*, 1959). The boundaries and internal subdivisions of this space are controversial subjects; whereas Mitchell (1950) was able not only to show that there was such a space but that it also has a central mid-line division, others, including Raper (1956), have not been able to demonstrate it satisfactorily.

Microscopically the plaques may consist of proliferating fibrous tissue, often infiltrated focally with lymphocytes, plasma cells or polymorphs, or of hyalinized collagen in which inflammatory cells are scanty (Raper, 1956; Hutch *et al.*, 1959; Stueber, 1959; Knowlan *et al.*, 1960). Small abscesses (Miller *et al.*, 1952) and arteriolitis (Ewell and Bruskewitz, 1952) have also been recorded.

The clinical manifestations are not limited to the urinary system and symptoms due to vascular obstruction are not uncommon (Ross and Tinckler, 1958; Hutch *et al.*, 1959). All the retroperitoneal structures tend to be compressed and distorted but the veins and some of the small arteries, and sometimes the ureters, may be invaded and partially or completely obliterated by the fibrous tissue. Ureteric involvement, though sometimes unilateral in the early stages, is almost invariably bilateral when the lesions are of any appreciable size.

The following case, treated several years ago at St. Paul's Hospital by Mr. Howard Hanley, illustrates the clinical and pathological features of the disease.

Case 1.—A 43-year-old man complained of malaise and pain in the back and was shown to have left ureteric obstruction. In July 1955 a hydronephrotic left kidney and 10 cm of ureter were removed, the ureter having been found adhering to the posterior abdominal wall at the level between the fourth and fifth lumbar vertebræ. There was mild non-specific pyelonephritis and in the greater part of the excised ureter the lumen was narrow and the wall was eccentrically thickened by a mass of chronically inflamed granulomatous tissue.

Right ureteric obstruction soon developed and on 26.8.55 a nephrostomy was performed. The patient remained in fair health for three years but was finally readmitted to hospital on 22.9.58, with a blood urea of 340 mg/100 ml, and died two weeks later. Since March 1957 there had been persistent œdema of the legs and thighs.

The immediate cause of death was pneumonia; a large retroperitoneal plaque was found, as well as amyloidosis of the right kidney, spleen, liver and arterioles. The plaque (Fig. 1) measured 18 × 9 cm and extended over the sacral promontory but did not involve the ureter immediately outside the bladder. Coils of bowel were adherent anteriorly, and it was firm and rubbery, between 2 and 3 cm in thickness and continuous posteriorly with the prevertebral fascia and the psoas muscles. Horizontal sections through the plaque revealed a dense mass of acellular collagen, diffusely and focally infiltrated with lymphocytes and

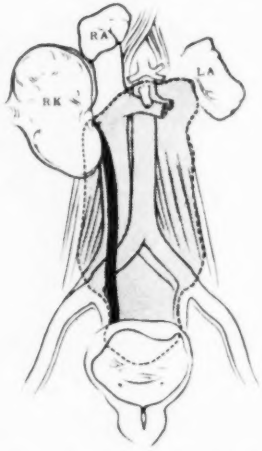

FIG. 1 (*Case I*).—Retroperitoneal fibrosis: The shaded area outlines the limits of the plaque found at autopsy. The thick continuous black line marks the course of the right ureter. R.K., right kidney. R.A., right adrenal. L.A., left adrenal.

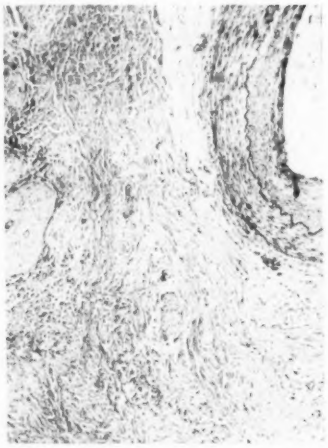

FIG. 2 (*Case I*).—Retroperitoneal fibrosis: The fibrous plaque lies between nerve trunks (on left) and one of the iliac arteries (on right) but does not invade either. × 40.

plasma cells, surrounding and compressing the arteries, nerves and lymph nodes (Fig. 2) and invading the vena cava (Fig. 3). The ureter was surrounded, though not invaded, but many small veins were completely obliterated.

Case I is a typical example of retroperitoneal fibrosis, although unique in that amyloidosis has supervened. There can be no doubt that this is a secondary phenomenon, because it was not found in the operation specimen and the tissue reactions are unlike those of primary amyloidosis (Symmers, 1956).

The two most important conditions to be considered in the differential diagnosis are retroperitoneal connective tissue tumours and the extremely rare peri-ureteritis plastica (Vest and Barelare, 1953), which most authors agree is distinct from the entity of retroperitoneal fibrosis, although several (Ross and Tinckler, 1958; Hutch *et al.*, 1959) believe that the two diseases may ultimately prove to be interrelated. Vest and Barelare's 4 patients all gave a history of urinary infection and had greatly thickened right ureters, due to a chronic inflammatory process affecting the peri-ureteral lymphatics. Characteristically the right ureter *only* is involved and, unlike retroperitoneal fibrosis, the thickening extends down to the point where the ureter enters the bladder.

The ætiology of retroperitoneal fibrosis is unknown and many theories have been put forward to account for the clinical and pathological findings. Those who believe that the disease is a renal fasciitis have searched their cases and the literature for evidence of previous infection in the areas whose lymphatics drain into the para-aortic nodes, which lie well within the fascial space (Harlin and Hamm, 1952; Chisholm *et al.*, 1954; Hutch *et al.*, 1959). Preceding intra-abdominal disease such as colitis or diverticulitis, although present in some cases, is not found sufficiently frequently to become established as a likely cause. The same may also be said of phlebitis of the ovarian and spermatic veins, as

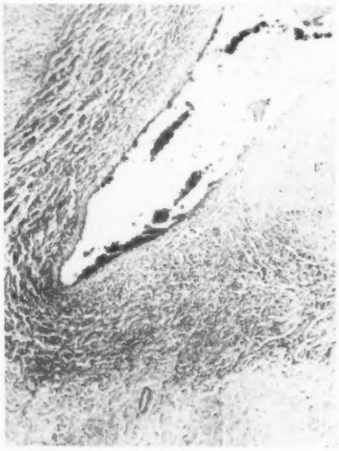

FIG. 3 (*Case I*).—Retroperitoneal fibrosis: A segment of the wall of the inferior vena cava showing a mass of collagen outside the vein wall (lower part of field) and replacing the muscle of the wall (top right). × 40.

suggested by Shaheen and Johnston (1959), although in Case I the maximum amount of cellular infiltration appears to be in and around the walls of some of the veins.

The fact that the cases were not described at all until only a few years ago has suggested that the process is an infection that has been modified by chemotherapy (Houston, 1957), although not all patients are on record as having received chemotherapeutic drugs prior to the onset of their illness. A recent report by de Gennes *et al.* (1960) of a patient in whom an abnormal serum electrophoretic pattern was found, with marked elevation of the alpha-2 and moderate elevation of the gamma globulins, may be of considerable significance as hyperglobulinæmia occurs, for example, in the generalized collagen diseases or in primary amyloidosis—which some believe to be a perverted form of antigen-antibody reaction.

In 1958 Hackett reported a fatal case and, because the para-aortic lymph nodes were rusty-brown in colour and contained much hæmosiderin, suggested that the fibrosis was due to organization of a hæmatoma. He further postulated that the bleeding might be arterial or venous and could result from quite minor degrees of trauma which may have preceded the onset of the clinical disease by many years. Although no siderosis of either the para-aortic nodes or of the plaque itself was found in Case I the evidence of vascular damage within the plaque indicates that Hackett's views are worth further study. Raper (1956) came to a similar conclusion and suggested that vascular damage might initiate some cases.

Peyronie's Disease

Peyronie's disease, or plastic induration of the penis, has been known for two centuries or more and indeed there is controversy whether de la Peyronie was the first to describe the condition in 1743 or whether the credit should go to Ephemerides in 1687 (Herbut, 1952). A vast literature has grown up but the ætiology is as obscure now as it was when the first cases were recorded (Callomon, 1945). Most of the accounts in the literature are concerned with the clinical features and various forms of therapy and many of them indulge in speculation—sometimes fanciful and often Rabelaisian—regarding the predisposing factors of this distressing condition. By contrast pathological reports are few and usually brief (*see* Polkey, 1928, for references).

The disease usually occurs in the fifth and sixth decades and is characterized by the appearance of fibrous lesions on the dorsum of the penis, causing angulation of the erect organ. Occasionally the elderly, or young men in their late teens, twenties or thirties, are affected and the youngest patient on record was only 18 (Polkey, 1928). The lesions occur in the tunica albuginea of the corpora cavernosa and sometimes also involve the underlying erectile tissue of the corpora or the deep penile fascia of Buck; they always lie beneath the deep penile vessels and nerves and the skin moves freely over them.

The condition is almost certainly more frequent than would be expected from a survey of the literature (Herbut, 1952) and Polkey (1928) collected reliable data on nearly 420 cases. Analysis showed that the lesions almost invariably occurred on the dorsum of the penis and in 24% of cases were situated near the symphysis; in 26% they involved the midshaft, in 22% were just behind the glans and in 14% affected the entire shaft. The exact location was not stated in a further 14% of cases.

Lesions may be single or multiple and commonly start as one or more nodes in the tunica albuginea just to one side of the mid-line. Adjacent nodes may coalesce in the long axis of the penis to form cords which may become an appreciable length. A cord or node may also extend laterally to form a plate over one of the corpora cavernosa, whilst fusion across the mid-line will produce saddle-shaped or "butterfly" plates. The commonest form is a lateral or saddle-shaped plate, and the next most common is a node or a wedge-shaped lesion in the septum between the corpora cavernosa. Linear strings sometimes occur and there are a few cases in which involvement of the whole circumference of the tunica albuginea produced a constriction round the shaft (*see* Polkey, 1928, for references).

The following case, recently under the care of Mr. John Sandrey at St. Peter's Hospital, illustrates the essential pathological changes.

Case II.—A 27-year-old married man attended hospital in November 1959 complaining of angulation of the erect penis and painful intercourse. A hard fibrous plaque 1·5 cm in diameter was palpable on the right dorsilateral aspect of the penile shaft just behind the coronary sulcus. A course of vitamin E had little effect and the lesion, which had not increased in size, was excised in January 1960.

The operation specimen was a flat plaque of tough white tissue, 1·5 × 2·0 cm, and between 0·3 and 0·45 cm in thickness. Some erectile tissue was attached to its undersurface and, although normal in the distal half of the specimen, was tougher and paler elsewhere.

Histological examination shows fusiform thickening of the tunica albuginea (Fig. 4) with loss of clear demarcation between it and the erectile tissue (normal appearances seen in Fig. 5). The bulk of the plaque consists of cellular fibroblastic tissue (Fig. 6) and in it a few capillaries are cuffed with lymphocytes. Where the plaque extends into the erectile tissue the septa are broadened and the smooth muscle is either vacuolated or has been replaced by collagen.

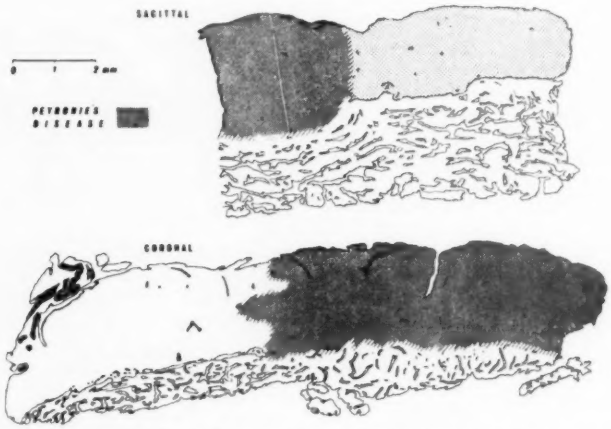

FIG. 4 (*Case II*).—Peyronie's disease: Camera lucida drawings of the plaque and the underlying erectile tissue of the corpus cavernosum. Unshaded area in lower diagram—normal tunica. Cross hatched areas—plaque of Peyronie's disease. Stippled area in upper diagram—appearances intermediate between those of plaque and normal tunica. Capillaries shown as black areas.

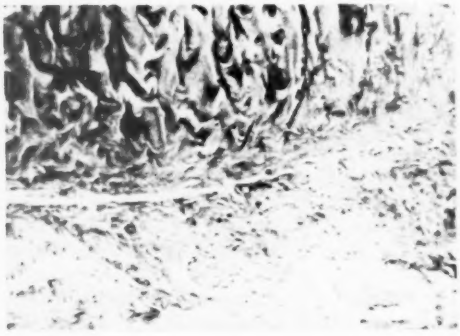

FIG. 5 (*Case II*).—Peyronie's disease: Normal tunica above and normal erectile tissue below. Note the sharp line of demarcation between the two, and the wavy appearance of the collagen in the tunica. × 70.

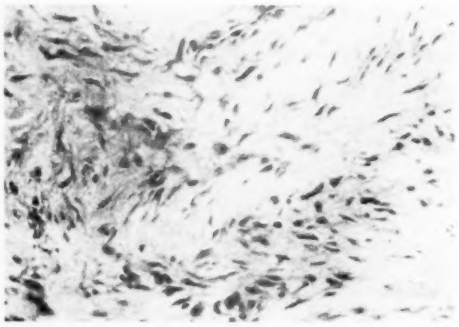

FIG. 6 (*Case II*).—Peyronie's disease: Cellular fibroblastic tissue, forming the mass of the plastic plaque. × 120.

A survey of the histological reports in the literature confirms that the lesions in this case are typical of Peyronie's disease—the only unusual feature, possibly, being the degree of involvement of the erectile tissue by the plastic plaque. In the recorded cases the changes vary from a predominantly spindle cell proliferation—with scanty vessels and minimal signs of inflammation—to a dense and compact fibrous tissue overgrowth which occasionally calcifies or ossifies (Kretschmer and Fister, 1926; Polkey, 1928; Burford, 1940; Johnson, 1940; Beach, 1941; Wesson, 1943).

The natural history of the disease is interesting and most cases develop insidiously and fairly slowly, reach a maximum size and then remain at that size—often for many years. There are several authentic cases of complete or partial regression without treatment, although this is by no means usual (Callomon, 1945). In the majority of the earlier case reports the disease was attributed to venereal infection, gout, arthritis, diabetes or arteriosclerosis but these are not now acceptable as specific ætiological factors (Callomon, 1945; Herbut, 1952). A more recent hypothesis that the disease is brought about by changes in the hormone balance of the patient (Heite and Siebrecht, 1950), clearly needs to be investigated further. There is also the view that the disease is in the nature of a fibrous

diathesis, and the similarity of the histological picture to that of keloid scars and Dupuytren's contracture is often quoted as supporting evidence. That there is a similarity is not in question and, as far as Dupuytren's contracture goes, it is more than a histological likeness because the not infrequent association of Peyronie's disease and the palmar contracture in the same patient is more than co-incidental (Callomon, 1945; Heite and Siebrecht, 1950; Waller and Dreese, 1952). Moreover the two diseases have common features in their natural history, both showing a tendency to slow insidious onset and progression to a certain point after which the lesion remains at a standstill. They differ, however, in that spontaneous regression occasionally occurs in the penile lesion but has never been recorded in Dupuytren's contracture (Callomon, 1945).

In both retroperitoneal fibrosis and Peyronie's disease there is an overgrowth of fibrous tissue occurring in specific and fairly well delimited sites. There are, moreover, many points of similarity between the two conditions but in neither is any real clue regarding their ætiology or interrelationship obtained from histological examination of surgical or autopsy material. True neoplasia and what might be termed straightforward inflammation can almost certainly be ruled out but there is a distinct possibility that a modified or atypical form of inflammation may be concerned.

Much the same problem regarding the ætiology confronted Barrett (1958) in the discussion in his paper on idiopathic mediastinal fibrosis. This again is a localized disorder although it differs from retroperitoneal fibrosis in that its boundaries are not within any recognized fascial compartment. Barrett makes the point that the generalized collagen diseases, such as polyarteritis nodosa, disseminated lupus erythematosus, rheumatic fever and rheumatoid arthritis, not only have a different histological picture to the localized ones, but are characterized by a systemic upset, fever, raised erythrocyte sedimentation rate, a tendency to joint manifestations and alterations in the gamma globulins in the serum. He separates the localized forms into two groups—the first comprising Peyronie's disease, Dupuytren's contracture and keloid scars and the second idiopathic mediastinal fibrosis, retroperitoneal fibrosis, pseudo-tumour of the orbit and Riedel's thyroiditis. In the former there are no systemic effects, the histological picture is more or less constant and they are all self-limiting diseases with fairly predictable clinical courses. The fibrous tissue has not the same density as in cases of mediastinal fibrosis, nor does it engulf adjacent structure. In the latter group there is again a basic histological similarity and in all there is a tendency for the fibrous tissue to surround adjacent structures and sometimes to invade the tissues in a manner that recalls the behaviour of a neoplasm. There is also a single case on record of a patient who died of mediastinal fibrosis and was found at autopsy to have retroperitoneal fibrosis as well (Tubbs, 1946).

It may well be that the localized forms of collagen disease are more closely related to each other and to the generalized forms than might be thought on the evidence at present available, but it is clear that none of them can be ascribed to a common ætiology or a common pathological process until many more patients have been subjected to a series of very thorough and comprehensive investigations.

REFERENCES

Barrett, N. R. (1958) *Brit. J. Surg.*, **46,** 207.

Beach, E. W. (1941) *Calif. West. Med.*, **55,** 7.

Burford, E. H. (1940) *J. Urol.*, **43,** 208.

Callomon, F. T. (1945) *Urol. cutan. Rev.*, **49,** 742.

Chisholm, E., Hutch, J. A., and Bolomey, A. (1954) *J. Urol.*, **72,** 812.

Ewell, G. H., and Bruskewitz, H. W. (1952) *Urol. cutan. Rev.*, **56,** 3.

de Gennes, L., Bricaire, H., Tourneur, R., and Cournot, L. (1960) *Lyon méd.*, **203,** 279.

Hackett, E. (1958) *Brit. J. Surg.*, **46,** 3.

Harlin, H. C., and Hamm, F. C. (1952) *J. Urol.*, **68,** 383.

Heite, H. J., and Siebrecht, H. H. (1950) *Derm. Wschr.*, **121,** 25.

Herbut, P. A. (1952) Urological Pathology. London.

Houston, W. (1957) *Brit. J. Urol.*, **29,** 28.

Hutch, J. A., Atkinson, R. C., and Loquvam, G. S. (1959) *J. Urol.*, **81,** 76.

Johnson, F. P. (1940) *Northw. Med., Seattle*, **39,** 22.

Knowlan, D., Corrado, M., Schreiner, G. E., and Baker, R. (1960) *Amer. J. Med.*, **28,** 22.

Kretschmer, H. L., and Fister, G. M. (1926) *J. Urol.*, **16,** 497.

Miller, J. M., Lipin, R. J., Meisel, H. J., and Long, P. H. (1952) *J. Urol.*, **68,** 447.

Mitchell, G. A. G. (1950) *Brit. J. Surg.*, **37,** 257.

Ormond, J. K. (1948) *J. Urol.*, **59,** 1072.

Pérard, J., and Orsini (1937) *Congr. franç. d'urol.*, **37,** 629.

Polkey, H. J. (1928) *Urol. cutan. Rev.*, **32,** 287.

Raper, F. P. (1956) *Brit. J. Urol.*, **28,** 436.

Ross, J. C., and Tinckler, L. F. (1958) *Brit. J. Surg.*, **46,** 58.

Shaheen, D. J., and Johnston, A. (1959) *J. Urol.*, **82,** 51.

Stueber, P. J., Jr. (1959) *J. Urol.*, **82,** 41.

Symmers, W. St. C. (1956) *J. clin. Path.*, **9,** 187.

Tubbs, O. S. (1946) *Thorax*, **1,** 247.

Vest, S. A., and Barelare, B., Jr. (1953) *J. Urol.*, **70,** 38.

Waller, J. I., and Dreese, W. C. (1952) *J. Urol.*, **68,** 623.

Wesson, M. B. (1943) *J. Urol.* **49,** 350.

Idiopathic Retroperitoneal Fibrosis Involving the Ureters [*Abridged*]

By F. P. Raper, F.R.C.S.
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The first examples of this disease were reported by Ormond (1948). In 1956 the author reported 7 cases (Raper, 1956); there were then only 10 previously reported cases. There are now 50 reported cases and personal reports to the author of almost another 70 suggest that this disease is not so uncommon as it at first appeared. With such an increased amount of information available a description of the disease entity becomes possible.

Site of the disease.—A consistent and puzzling feature of the disease is the site of the fibrosis. Although its extent may vary, its centre is almost always at the level of the fourth and fifth lumbar vertebræ, overlying the aortic bifurcation. The ureters are at the edge of the lesion and are always pulled towards the mid-line (Fig. 1). The width

Fig. 1.—Diagram traced from a radiograph of a patient with retroperitoneal fibrosis showing its characteristic position with the ureters involved at each edge.

of the fibrotic area is sometimes no greater than the width of the vertebral bodies. To describe it as peri-ureteric fibrosis ignores the fact that the disease probably arises in the mid-line. The thickness of the fibrous tissue varies from one patient to another and may form a palpable swelling, but more often is described as a plaque or fibrous mat. It may be noticed during a laparotomy as white scars in the base of the mesentery. It may compress or distort the aorta or vena cava, and in one case reported by the author obstructed the common bile duct.

The histology of the fibrous tissue has been described already by Dr. Pugh.

Symptoms.—Most patients have been under the care of a doctor for a few weeks or months before a diagnosis is made. The common symptoms are ill-defined pains and some of the early symptoms such as nausea, weakness and loss of weight may be the result of developing uræmia. Eventually and sometimes with disconcerting speed the patients develop renal pain with or without oliguria. Until these final symptoms, disturbances of micturition are uncommon. In retrospect other symptoms may be considered significant such as claudication or œdema of the legs due to interference with the circulation. Intermittent testicular pain is not uncommon and may be due to involvement of the spermatic vessels.

Clinical examination does not usually aid the diagnosis but there may be a palpable tender kidney or central abdominal tenderness.

Diagnosis by radiography.—This disease has a characteristic pyelogram, the essential features being an obstruction of one or both ureters in their middle third with the ureter or ureters drawn towards the mid-line in the obstructed area (Fig. 2). If the ureter is incompletely obstructed there will be a hydronephrotic kidney above the block, whereas if the block is complete the kidney is often small and functionless (Fig. 3).

Treatment. — Cortisone: The fibrinolytic properties of the corticosteroids make them an attractive group of drugs to use in a disease of this type. However, there are few reports of their use and even these do not conclusively prove their value. I am indebted to Mr. J. F. S. Withycombe for his detailed personal reports of 2 patients in whom prednisone was used to such good effect that it seems only reasonable to suggest its use for other patients. The first patient had previously had a left nephrectomy and was in hospital for investigation of a right hydronephrosis due to retroperitoneal fibrosis when he developed a very painful attack of herpes. To relieve this pain he was given 20 mg of prednisone daily for six weeks. Another intravenous pyelogram showed very considerable improvement in the right hydronephrosis. There has been no deterioration during the following eighteen months. The second patient was admitted to hospital three months after a partial gastrectomy because that operation had not relieved his symptoms and he was persistently vomiting. After a short time in hospital he developed oliguria and renal failure and was too ill for complete investigation. On a provisional diagnosis of polyarteritis nodosa he was given prednisone (80 mg daily dropping to 15 mg daily). There was a dramatic improvement in

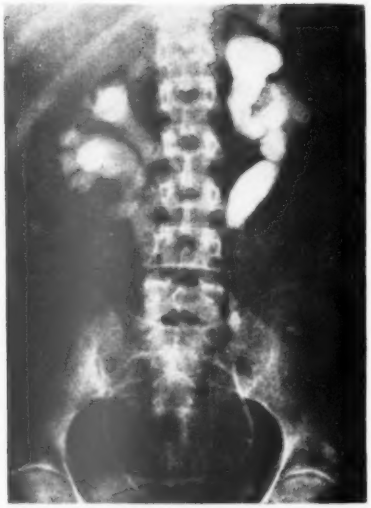

FIG. 2.—Bilateral ascending pyelogram showing bilateral hydronephrosis with a narrow segment at about the centre of each ureter, this area of ureter being closer to the mid-line than normal.

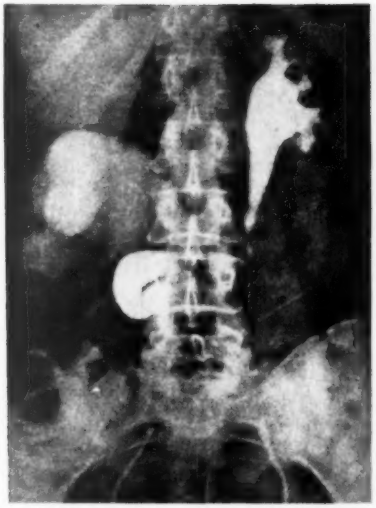

FIG. 3.—Bilateral ascending pyelogram showing a large right hydronephrosis and a small left kidney. Fifteen months earlier both kidneys were hydronephrotic but the left has now ceased to function. The medial position of the narrow segment of the ureters is again seen.

his condition with a diuresis and fall in the blood urea. This allowed a full urological investigation which revealed no function of the left kidney and a right hydronephrosis. Later exploration of his left ureter confirmed the diagnosis of retroperitoneal fibrosis, and with further steroid therapy the right hydronephrosis returned to normal.

Relief of the uræmia: In these patients an attempt will probably be made to get a catheter up one or other ureter when investigating the sudden onset of anuria. The catheter may pass up to the kidney without much difficulty for the envelopment of the ureter in a rigid tunnel seems to prevent conduction of urine even before a complete mechanical obstruction has occurred. If a catheter can be passed to the kidney and a good flow of urine results it should be left there to relieve the uræmia. If no catheter can be passed the uræmia should be relieved by dialysis with an artificial kidney or a nephrostomy on the tender kidney.

Ureterolysis is a satisfactory way to treat the ureteric obstruction and in most patients the ureter can be dissected from its bed of fibrous tissue. An approach from the flank is usual but mid-abdominal exposure has the advantage that both ureters can be freed at the same time. It also reveals more accurately the exact site of the disease, and from further observation of this it may be possible to learn more about its cause.

When the ureter has been set free from the fibrous tissue it should be fixed in the iliac fossa by stitches between the posterior peritoneum and the muscles of the posterior abdominal wall medial to the laterally placed ureter. The ureter may be brought within the peritoneal cavity and so far this does not seem to have been followed by any trouble. In one patient, after dissecting out the ureter, there remained a few nodules of fibrous tissue in the wall of the ureter. These nodules have not grown in the succeeding seven years.

Prognosis.—The prognosis of this disease can only be assessed by observations over many years. One of the author's patients died from renal failure eleven years after the first symptoms of the disease. Others previously reported (Raper, 1956) are still alive and in none has renal failure or ureteric occlusion advanced. One has had a leg amputated because of severe ischæmic pain and it is possible that vascular occlusion by the retroperitoneal fibrosis played some part in this. Another has developed severe claudication in both legs at the age of 49.

Acknowledgments.—The author wishes to thank Professor L. N. Pyrah for permission to include his patients in the above review and Mr. J. Hainsworth of the Photography Department, St. James's Hospital, for the preparation of the illustrations.

REFERENCES

ORMOND, J. K. (1948) *J. Urol.*, **59**, 1072.
RAPER, F. P. (1956) *Brit. J. Urol.*, **28**, 436.

Peyronie's Disease

By A. Ashworth, F.R.C.S.
Manchester

Painful curvature of the erect penis and the presence of hard nodules in the shaft of the penis form a group of symptoms to which the name Peyronie's disease has been given. It is also commonly known as plastic induration of the penis and fibrous cavernositis.

De la Peyronie described the condition over two hundred years ago and gave a detailed account of 3 cases out of the many that he had seen. He noted the bead-like nodules on the dorsum of the penis and deduced that they were the cause of the upward bend which the phallus assumed on erection. He thought that the condition was often, but not always, associated with a past history of gonorrhœa or syphilis and that it was useless to treat the nodules before eradicating the "virus vénérien". When this had been achieved by a prolonged course of mercurial inunctions he advocated partaking of, and bathing in, the waters of Barège.

There are very few references in the British or American literature to this particular type of painful chordee until the last quarter of the last century. In 1875 Van Buren and Keyes described two conditions which they called calcification of the penis and chronic circumscribed inflammation of the erectile tissue of the corpora cavernosa which had hitherto not been accurately described, and gave details of 5 cases. For the next forty years this symptom complex was often referred to as Van Buren's disease but it is apparent from Van Buren's account that his patients were afflicted with a condition which Peyronie had described one hundred and thirty years before.

Since those days many forms of treatment have been tried but no single method has gained general acceptance. The condition is not rare but little is known about its essential cause and there is scant information concerning the natural history of the disease.

My series consists of 32 patients. I have followed up as many as possible to see if anything can be learned about the cause of the disease and to discover what benefit, if any, has been received from treatment. All the patients were seen in the departments of urology at Salford Royal Hospital, The Christie Hospital and Crumpsall Hospital, Manchester, and most of them were under the care of Mr. D. S. Poole-Wilson to whom I am indebted for permission to include his patients in this survey.

Symptoms and signs.—The youngest patient was 29 and the oldest 68 years of age (Fig. 1). The average was 52 and this agrees with other series (Burford *et al.*, 1951; Lowsley and Boyce, 1950). The average duration of symptoms was six months with extremes of five days and several years.

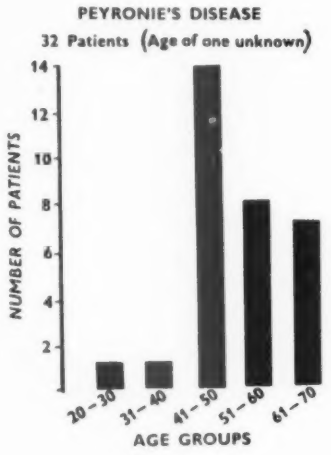

Fig. 1.

The patient usually reports that although the penis is normal when flaccid, suddenly and for no apparent reason it has become bent and painful on erection and, as a consequence, intercourse is difficult or impossible. Neither of these symptoms is invariably present: a quarter of our patients experienced no pain and 2 were quite certain that the phallus was not deformed. Often the patient has discovered a lump or area of thickening in the penis and sometimes this is regarded with great anxiety as a manifestation of cancer or venereal disease.

On examination the penis looks normal but palpation reveals one or more fibrous nodules or plaques in the tunica albuginea of the corpora cavernosa. The nodules are situated as a rule on the dorsal or lateral aspects of the corpora; less commonly they are found on the ventral surface or deep within the penis in the pectiniform septum. Often it is difficult to determine their exact site. In some cases the nodule merges gradually into the surrounding normal tunic but as a rule it is more button-like and possesses a well-defined

edge. There is no fixation of the skin over these areas and tenderness is usually absent. With the passage of time the nodules may shrink or even disappear but sometimes the disease progresses and fresh nodules develop or the original ones increase slowly in size. There is no case in this series, and I have seen none described in the literature, in which the nodularity has been found in the enveloping tunic of the corpus spongiosum.

Ætiology.—It was natural that the early writers should regard the condition as a sequel to venereal infection or an expression of a gouty or rheumatic diathesis, but these views were gradually discarded. In 1894 Jonathan Hutchinson wrote: "Now and then there is, as we might expect, a history of syphilis in youth; and very often there is, as also might be expected, a history of gout in the family. It is but seldom, however, that either the one or the other of these affections appears to be definitely connected with the symptom." Nor have we any reason to dissent from that view now.

However, there is another condition with which Peyronie's disease often seems to be associated — Dupuytren's contracture — and 5 patients in this series were found to be so affected (Table I). The coexistence of the two

TABLE I.—PEYRONIE'S DISEASE (32 PATIENTS)

Diseases which preceded or accompanied Peyronie's disease	
Dupuytren's contracture	5
Chronic mastitis	1
Tuberculosis	4
Renal stones	1
Actinomycosis of jaw	1
Gonorrhœa	1
Non-specific urethritis	1

lesions in the same patient has been noted on many occasions but Heite and Siebrecht (1950) offered statistical proof that the association was found more often than could be accounted for by chance alone. This work appears to support the often propounded theory that both Peyronie's disease and Dupuytren's contracture are due to a tendency to generalized dysplasia of fibrous tissue.

Trauma has also been regarded as a possible cause and in 2 of our patients the onset of symptoms was attributed to an injury sustained a short time previously.

It has been stated that repeated minor traumata, unnoticed at the time, and sustained during excessive or difficult sexual intercourse, may play an important part in the cause of the disease by producing minute hæmorrhages, which ultimately become fibrosed, in the tunica albuginea. Sexual hyperactivity may be a precipitating factor in some but certainly not in all cases. 2 of our patients were bachelors whose sexual experience was very limited and 5 others said they had remarked an appreciable loss of libido for some years previously. I suggest that although trauma sustained in coitus may have some ætiological significance the marked increase in incidence of the disease in middle life and its rarity in the young indicate that some underlying abnormality of the tunica is of greater importance.

Treatment.—Numerous authors have reported a modicum of success with many forms of treatment and some have claimed that a high proportion of their patients have been "cured" or "greatly improved" but do not always specify what is meant by these terms. Pain is the symptom most easily relieved but it is difficult to assess improvement in individual symptoms as they are to some extent interdependent and both pain and chordee may improve as a result of continued diminution in strength of the erection and not because treatment has been effective. In some instances, however, the start of treatment is followed sufficiently rapidly by relief of pain for us to be justified in regarding this as cause and effect.

Before the value of treatment can be assessed it is necessary to know also how the untreated disease progresses. There are 11 untreated patients in this series but no useful information can be gained from 3 of them because the follow-up is so short. The remaining 8 patients have been under observation for periods of up to five years; their ages vary from 41 to 57. None has normal function: 2 are impotent and the other 6 say that although coitus is possible it occurs at very infrequent intervals and the erection is maintained only with considerable difficulty—intercourse is regarded more as a duty than a pleasure. In all cases the pain and chordee diminished as the sexual urge became weaker. In one man the fibrous thickening in the tunica albuginea increased in size and fresh areas of fibrosis appeared during the two years that he was under observation; in 2 patients the nodules have disappeared and in 2 others shrunk considerably. It seems, therefore, that although the process of fibrosis may sometimes be self-limiting and, in fact, capable of spontaneous regression the onset of Peyronie's disease heralds the end of effective sexual life.

The great number of drugs that have been tried at one time or another indicates that none has been completely satisfactory. The only two that I wish to mention are vitamin E and cortisone both of which have been used extensively because of their ability to resolve fibrous tissue. Dahl (1954) has reported on a number of patients to whom he gave mixed tocopherols or concen-

trated wheat germ oil in doses of 300 mg daily for as long as improvement continued—usually about nine months. Marked improvement was obtained in a quarter of his cases. 6 of our patients were given vitamin E but not in such large doses or for so long a period as Dahl recommends; 1 patient was relieved of his pain. My first experience with cortisone was most encouraging. The patient was given 100 mg daily for a month and a gradually diminishing amount for another four weeks. Mid-way through treatment some improvement was noted and this continued during the ensuing twelve months. At present, six years after treatment, there is slight residual curvature but the fibrotic thickening cannot be felt and he is functionally normal. It may be significant that he is the youngest patient in the series. 4 more patients have been treated similarly but not with such a gratifying result; one man was relieved of pain within a fortnight but the others derived no benefit. Teasley (1954) seems to have been one of the first to inject hydrocortisone direct into the fibrous plaques and his results were fairly encouraging. Furey (1957) by using this method obtained fair to excellent improvement in 5 out of 14 patients. Both Teasley and Furey say that pain is easier to cure than the curvature.

Excision of the nodules is strongly recommended by Lowsley and Boyce (1950) who report a cure in 58%, and marked improvement in 20% of 50 cases so treated. The operation is carried out in a bloodless field using a tourniquet and the gap resulting from the excision of the fibrous tissue is plugged with a pad of fat. Only one of our patients has been submitted to operation and the result is most unsatisfactory.

In many centres radiation therapy has been employed. Burford *et al.* (1951) have published an account of 124 patients treated by radium; 76%–80% of these were cured or improved, the higher rate being obtained if vitamin E was given in addition. Dahl (1954) on treating 96 patients with radiation had the same degree of success that he had obtained with vitamin E and says that cases treated unsuccessfully by one method have sometimes improved when the other has been tried. At the Christie Hospital beam-directed X-ray therapy is preferred to radium as it is very difficult if not impossible to give complete protection to the testes when radium is applied to the penis. A 250 kV machine is used and the beam is projected laterally at the penis which is supported in an upright position, the testicles being shielded with a lead sheet. In general, the condition has been treated in the same way as a keloid scar, a relatively high dose (500r) being given in a single treatment and then repeated two to three times at intervals of a few months. A few patients have been given a much lower dose (100r) at weekly intervals for eight to ten weeks. In neither method is the dose large enough to bring about skin changes. 11 cases were treated in this manner but 3 were lost to follow-up a few weeks after the cessation of treatment. Of the other 8 patients one, aged 46 when treatment was started, now has normal sexual function twelve years later and there is only very slight chordee and thickening of the tunica. 3 patients experienced very rapid relief of pain but 1 has since become impotent and there is no information concerning sexual function in the other 2. 4 have received no benefit.

It is unreasonable to expect a single form of treatment to be applicable to all cases; in fact, treatment is often not necessary. If the onset of Peyronie's disease is clearly the final episode in the waning sexual powers of a middle-aged or elderly man, and pain is not troublesome, treatment is both unnecessary and futile. If pain is a prominent feature of the disease then radiation therapy may be helpful. In a younger or more vigorous man cortisone either by mouth or injection locally may be beneficial, and if this fails a combination of X-ray therapy and vitamin E is well worth trying. Whatever treatment is used it must be accompanied by the assurance that the condition is in no way dangerous or injurious to health.

REFERENCES

Burford, E. H., Glenn, J. E., and Burford, C. E. (1951) *Urol. cutan. Rev.*, **55**, 337.

Dahl, O. (1954) *Acta radiol., Stockh.*, **41**, 290.

Furey, C. A. (1957) *J. Urol.*, **77**, 251.

Heite, H. J., and Siebrecht, H. H. (1950) *Derm. Wschr.*, **121**, 25.

Hutchinson, J. (1894) *Arch. Surg., Lond.*, **5**, 329.

Lowsley, O. S., and Boyce, W. H. (1950) *J. Urol.*, **63**, 888.

Peyronie, F. de la (1743) *Mem. Acad. roy. Chir.*, **1**, II, 318.

Teasley, G. H. (1954) *J. Urol.*, **71**, 611.

Van Buren, W. H., and Keyes, E. L. (1875) On the Genito-Urinary Organs. London.

BOOK REVIEWS

Symposium on Glaucoma. Edited by William B. Clark, M.D., F.A.C.S. (Pp. 314; illustrated. 101s. 6d.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1959.

The symposium opens with a chapter by Dvorak-Theobald on the histology of tissues surrounding the angle of the anterior chamber, and this is followed by a chapter on pathology. A series of illustrations shows the changes which are to be expected in the collagenous tissue of the trabeculæ and sclera. Swann contributes a chapter on surgical anatomy in relation to glaucoma, and there are many practical details with regard to incisions made at the limbal area with a view to producing filtration. He also has a chapter on the miotic treatment of glaucoma, reviewing the current concepts of hypotensive mechanisms, and includes a classification of miotic drugs in accordance with their pharmacological effects. Bernard Becker writes a chapter on aqueous production and flow, and another on provocative tests and their effect on tonography. The first is largely biochemical, showing the excellent agreement obtained by completely independent approaches to the problem of estimating the rate of secretion of aqueous humour, and the second evaluates the various provocative tests to show that, combined with tonography, they provide a useful addition to established methods for early detection.

Morton Grant discusses aqueous production and flow in the normal and glaucomatous eye, and the factors affecting them, and he contributes a further chapter on basic tonometry and tonography, dealing with the sources of error and the influence of scleral rigidity. Maumenee classifies the glaucomas and discusses the question of good medical control, pointing out that in open-angle glaucoma the patient is treated medically until the tension becomes obviously out of control or there is loss of visual function due to the disease. The surgical treatment of chronic simple glaucoma is described, giving the indications for surgery and stressing conservatism. Haas discusses surgery for angle-closure glaucoma. There are further chapters on acetazolamide and other inhibitors of aqueous secretion, on modification in the technique of filtration operations, on surgery for congenital glaucoma and on miscellaneous topics such as hypersecretion and low-tension glaucoma, combined forms of the disease, glaucoma associated with cataract and venous occlusion, glaucoma in the Negro and in the diabetic patient.

The book closes with a round-table discussion recorded in some sixty pages, when questions are asked by the chairman and each contributor replies. The volume presents in clear form the present-day position of glaucoma in all its aspects, with emphasis on practical considerations. Gonioscopy is discussed in detail and there is a chapter by Zimmermann on the presence of a hyaluronidase-sensitive acid-muco-polysaccharide in the trabecula and iris. The significance of this material in the angle of the anterior chamber is still speculative, but it may play a critical role in regulating the metabolism of inorganic iron and water. Many lines of enquiry which are being followed at the present time in an attempt to bring the syndrome of glaucoma under rational control are discussed. The book is beautifully produced and is a credit to American ophthalmology.

Recent Research in Freezing and Drying. Edited by A. S. Parkes, C.B.E., F.R.S., and Audrey U. Smith, D.Sc., M.B., B.S. (Pp. vii + 320; illustrated. 63s.) Oxford: Blackwell Scientific Publications. 1960.

This is a report of the Second International Symposium on Freezing and Drying, which was held in 1958. The subjects discussed include the biophysics of freezing and freeze-drying, and the effect of these processes on viruses, bacteria, trypanosomes, yeasts, spermatozoa, and mammalian tissues including human cornea, bone and blood vessels. Though many questions remain unanswered there have been important advances, especially in relation to the long-term storage of living cells and tissues, and the book is thus a mine of information which will be welcomed by workers in many fields. It suffers, however, from the defect that very little discussion is included and the various contributions are presented as isolated papers without any attempt being made to link them together. As with many symposia those who were not present would gain enormously if someone who was would write a critical review of the proceedings as a postscript to the formal papers.

Lectures on the Scientific Basis of Medicine. Vol. 7, 1957–58. British Postgraduate Medical Federation, University of London. (Pp. xi + 496; illustrated. 45s.) London: University of London, Athlone Press. 1959.

The latest volume of this series maintains, in fulfilling a much-needed function, the high standard of its predecessors. This function is to provide the ordinary medical reader with a balanced and authoritative presentation of some of the numerous aspects of fundamental knowledge which are advancing apace; advances that

carry with them present and future implications for the practice of clinical medicine.

No one who wishes to be abreast of his subject can neglect many of the subjects collected in this and in the previous volumes, although naturally some are of less relevance to his individual work than are others. Genetics, for instance, have recently taken on a new significance for the practising doctor, and thus he will welcome the lectures on biogenetics and medicine and on blood group genetics. Immunity and auto-immunity are subjects of much present interest, and here there are chapters on lymphoid tissue and on acquired hæmolytic anæmia.

The connective tissue disorders are no longer so rarely recognized as to be of little practical relevance, and some of the relevant basic facts are found in the chapter on the structure and stability of collagen. DNA, due to the B.B.C. Television Service, is now a talking point, and the chapter on the growth of viruses will enable the doctor for once to out-talk his patients.

There are many more examples that could be quoted; each of the remaining eighteen chapters in fact.

The Arterial Wall. Edited by Albert I. Lansing, A.B., Ph.D. Sponsored by The Gerontological Society, Inc. (Pp. ix + 259; illustrated. 60s.) London: Baillière, Tindall & Cox, Ltd. 1959.

It is appropriate that Dr. Abraham Dury in his "summation", i.e. summary, to this interesting book should remind us that Lyman Duff once said that the literature on atherosclerosis might well suggest that the process is "so independent of the substrate of the vessel wall that it may occur in the absence of the blood vessels themselves". Although its contents do not wholly confirm Duff's *obiter dictum*, they do go some way towards it; giving the impression of the seeker, armed with electron microscopes, ultracentrifuges and electrophoretic apparatus, groping through verbal mazes towards the elementary facts of arterial structure and function. The mountains have certainly been in labour—and yet the *ridiculus mus* is not altogether an unsubstantial creature. It is the conflict between morphology and biochemistry, with the lack of clarity in the shadow line between them, that excites but at the next turn depresses the reader.

The chapters on the vasa vasorum, the vascular endothelium and elastic tissue are comprehensive and readable, but those on the biochemistry and physical chemistry of the arterial wall are less convincing and more speculative. One wonders to what extent chemists have a conception of the intricate interweavings of the different constituents of the structures they are dealing with, and of the way in which the proportions of these vary with sites, to say nothing of their pathological variations in disease and their changes with age. The chapters on the lipid metabolism of connective tissue in relation to the ageing of vessels, and on the metabolism of the arterial wall, are courageous attempts to deal with these imponderables—but, when all is done and said, only a fraction, and that a small one, of much of this part of the work is directly concerned with the arterial wall itself, and much of the data are drawn from the study of the participating tissues in other sites. This is a book which will interest most of those who are working upon arteries. It is a brave attempt and stimulating, and contributes something to the slow growth of knowledge. The Americanization of the English language across the Atlantic has so progressed that certain paragraphs almost require translation.

Henry E. Sigerist on the History of Medicine. Edited by Félix Marti-Ibáñez, M.D. (Pp. xviii + 313. $6.75) New York: MD Publications, Inc. 1959.

This volume, which consists of a carefully chosen selection of the author's very numerous articles, is indeed a remarkable work, in which the subject is treated from an aspect quite different from that apparent in the traditional textbooks of medical history. As the editor observes: "From his earliest works, Sigerist knew how to get away from the narrow ambit of history considered as a mere chronology of dates on a single subject, so as to link medicine with the civilization of each epoch."

The 27 essays which the book contains deal with a great variety of subjects, all historical in the broadest sense of the word, but all exhibiting the author's intense interest in humanity, which was without doubt the outstanding feature of his personality and the mainspring of all his writing. This is evident in the very first chapter, "The Physician's Profession Throughout the Ages", which seems to us to summarize more or less the author's message to his fellow-men.

A scholar, a remarkable linguist, and a philosopher from his earliest years, a Doctor of Medicine later in life—and this may be said to have been an afterthought—Sigerist has left us a contribution to medical history and philosophy as striking and interesting as it is unusual. We commend this book to the notice of all, medical and non-medical readers alike, who appreciate original thinking and a broad outlook on the story of the development of medicine from the earliest times.

Alcoholism. Edited by David J. Pittman, Ph.D. (Pp. xviii + 96. 30s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

In the U.S.A. there are said to be five million alcoholics and the disorder is said to cost the community some $736 million annually. In an effort to study the problem further, the Social Science Institute of Washington University, St. Louis, Mo., has co-operated with medical men. This book sums up briefly what is known about alcoholism from the standpoint of experts in different disciplines. Professor Jackson Smith discusses the psychiatric approach and how the alcoholic can be treated at an earlier stage. Professor Ebbe Hoff deals with the metabolism of alcohol in the normal and in the alcoholic. Professor Snyder, of Yale, indicates some interesting exceptions to the rule that the amount of alcoholism is proportional to the amount of alcohol consumed in a community. Emphasis is on what is not known rather than what is known, and pointers are given to the most promising lines of research that might be undertaken. This is a small but useful contribution to a public health problem, and is indispensable to any group contemplating a research project on the subject.

The Roots of Crime. Vol. 2 of Selected Papers on Psycho-Analysis. By Edward Glover, M.D., LL.D. (Pp. xiii + 422. 45s.) London: Imago Publishing Company Ltd. 1960.

"I do not conceal my view that the most fundamental approach to crime, pathological or otherwise, is that of psychoanalysis." Thus, in the preface to his book, does Dr. Edward Glover make his position clear, though his abundant writings and personal distinction have made it clear already. To restrict further the elect few who may examine and report on the delinquent, Dr. Glover says at p. 363: "It is absurd to think that a general training in psychiatry . . . enables anyone to speak with authority on a complex problem . . ."—referring to criminals. Perhaps only a few will agree that the psychiatric study of delinquency is beset by so many difficulties that it should be entitled "to be regarded in the strict sense of the term as a 'specialty' in its own right".

This is a thoroughly modern and yet a comprehensive volume, including an essay written in 1922, and yet making reference to the Wolfenden Report and the Bill (now an Act) dealing with street offences. It is written with the clarity and felicitous syntax associated with Dr. Glover's name, and to the psychoanalyst it will be a treasured record of his thought over a period of nearly forty years. It is indeed interesting that the 1922 essay reads as if it had been written yesterday.

At the same time, for one who is not a psychoanalyst this book is not so much a treasure as another obstacle to be demolished in the process of constraining acceptance of psychiatry by colleagues, by magistrates and the world at large. Dr. Glover could never be accused of muddled thinking, but perhaps his deep-rooted and sincere beliefs have adversely influenced his judgment. Why for instance (p. 267) should it be regarded as an instance of "ambivalence of the State" that a first offender should be warned and helped, while an incorrigible one is punished? This change of attitude in the light of experience is usual in the family, in the schoolroom and in the office, and is surely not confined to the Courts. Again (p. 15), "The factor of unconscious symbolism in theft arouses considerable scepticism amongst lay readers". Indeed it does, and not only among lay readers. Your reviewer was recently burgled, and symbolism of any sort appears to have played very little part in the burglar's selection. With a simplicity that psychoanalysts do not always follow, he settled for such few objects as appeared to be of value!

For one whose mind is not yet made up in the matter of the role psychoanalysis has to play in treating criminals, it would be difficult to find a clearer exposition of existing thought than this. The index is full, the presentation agreeable and the price, by modern standards, is reasonable.

A Synopsis of Fevers and Their Treatment. Revised by James H. Lawson, M.D. (Glas.), D.P.H. 10th edit. (Pp. viii + 184. 10s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

The appearance of a tenth edition of this little manual is sufficient tribute to its usefulness. As it is ten years since the ninth edition appeared, the advances in treatment which have been made in that period have necessitated almost complete re-writing and a number of additions. Whilst the necessity for some selection of material in a "synopsis" is obvious, the reasons for omitting any mention of such important fevers as influenza and undulant fever are not clear. Differential diagnosis is, moreover, dealt with rather cursorily in many cases.

The section on antibiotics is well done, but some general statement as to the *aims* of antibiotic treatment would have been helpful. Advice as to the dangers of over-dosage and also the importance of being prepared for severe anaphylactic reactions might have been more emphatic.

In the final short chapter on the control of

infectious diseases a special reference to milk as a carrier of infection deserved inclusion.

A Handbook of Diseases of the Skin. By H. O. Mackey. 6th edit (Pp. 263; illustrated. 8s. 6d.) London: Macmillan & Co. Ltd. Dublin: C. J. Fallon Ltd. 1959.

There can be no doubt about the popularity of this book which has reached its sixth edition in seven years. Its popularity is due largely to its very low price and the large number of excellent photographs. There are rather more than 200 illustrations including many rarities (there are no less than 5 illustrations of urticaria pigmentosa) but some common conditions such as pityriasis rosea are not illustrated.

The book is fairly comprehensive but the descriptions of disease are not very precise. It is not clear what erythema multiforme, for example, looks like or how frequently it occurs. Nor will many agree that in pregnancy it is a sign of grave toxæmia. Treatment is also not entirely satisfying. For example, no mention of antihistamine drugs is made in the discussion on the treatment of chronic urticaria.

Parasites and Parasitic Infections in Early Medicine and Science. By R. Hoeppli, M.D., D.Sc. (Pp. xiv+526; 23 plates. 63s.) Singapore: University of Malaya Press. London: Oxford University Press. 1959.

The author of this book had a practically illimitable task when he undertook to describe the early history of parasites and of the diseases they either caused or were thought to cause; few people could have been more capable of straying down the obscure byways of classical and non-European literature or legends necessary for such a work, but Professor Hoeppli was particularly qualified by his linguistic ability and his long residence in the East. Thus a book of fascinating and unique interest has been produced, written in a style completely its own, in some ways repetitive, as if the author had become semi-asianized himself; at times the reader also almost comes to believe in the old doctrines of spontaneous generation, the vital force or aura, the macrocosm and microcosm which dominated the ancient "physicians" from one end of the world to the other, and coloured all their observations on parasitology. It is remarkable how alike were the beliefs held by peoples as far apart as China and Greece, or India and Rome.

It is easy to find one's way through this historical maze in Hoeppli's book because each chapter or section contains a résumé, conclusions, summary, notes and references—one is drawn from the résumé to read the detail in the text, to look up the reference or note, and then perforce to search for the original in Ebers Papyrus or Hippocrates, &c.

The first half of the book is devoted to the history of helminths and arthropods; and also to the ideas about what we know now to be diseases caused by protozoa. A short section describes the development of the modern outlook in the last three centuries resulting from the discovery of the microscope. There is also a detailed account of the Chinese outlook on certain important conditions such as malaria, dysentery, drugs, lice and scabies. Some interesting plates taken from old books and documents illustrate the common parasites mentioned in the text.

The author suggests that his book is only a collection of material for a history of parasitology; this is much too modest, and biologists of all kinds will find it illuminating and useful.

Principles and Methods of Clinical Chemistry for Medical Technologists. By Eugene W. Rice, Ph.D. (Pp. xvii+286. 56s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960.

This book sets out to explain the fundamental principles behind common hospital chemical laboratory procedures, to describe something of the application of the results obtained to clinical medicine, and finally to describe the technique of some commonly used analytical methods. The book is designed for technologists, or in more common parlance on this side of the Atlantic, for technicians. The aim is an admirable one, for a good technician will certainly want to know more about the estimations he performs than the mere "recipe". However, it is not clear what level of knowledge in the basic sciences is expected from the reader, since in one chapter it was felt necessary to explain the metric system, while a few pages later a complicated example is given of balancing "redox" equations which would certainly not be understood by a complete beginner. The same applies to the three dimensional structure of E.D.T.A., and to a complicated exposition of Beer's law. The section explaining the application of results is on the whole good, though necessarily sketchy, and it seems wrong in a book of this kind that only four lines should be devoted to the role of sodium in the body whilst a discussion of magnesium covers a page and a half. The methods are clearly expressed and easy to follow but sometimes outmoded. In spite of the criticisms the technician should find this book useful in conjunction with an elementary textbook of chemistry, although it is doubtful if, by itself, it would be adequate for the I.M.L.T. examinations.

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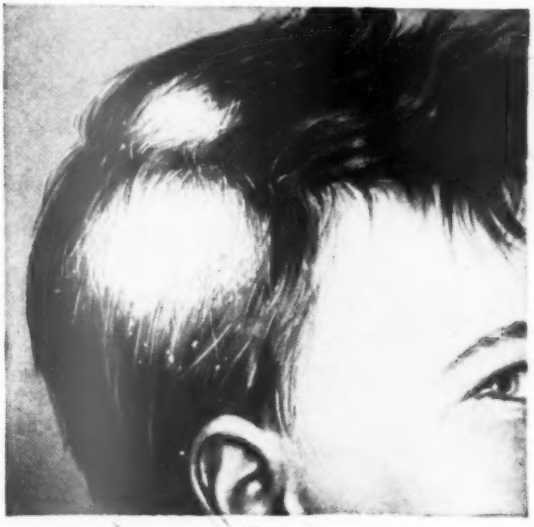

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